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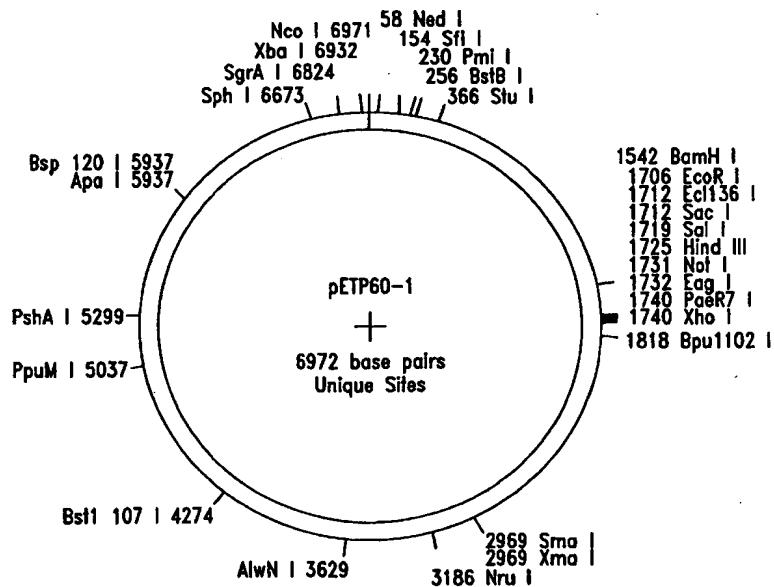
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(54) Title: STREPTOCOCCAL HEAT SHOCK PROTEINS OF THE HSP60 FAMILY



(57) Abstract

Methods and compositions comprising isolated nucleic acid molecules specific to *Streptococcus pneumoniae* and *Streptococcus pyogenes*, as well as vector constructs and isolated polypeptides specific to *Streptococcus pneumoniae* and *Streptococcus pyogenes* are provided. Such compositions and methods are useful for the diagnosis of Streptococcal infection and for generating an immune response to Streptococcal bacteria.

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STREPTOCOCCAL HEAT SHOCK PROTEINS OF THE HSP60 FAMILYTECHNICAL FIELD OF THE INVENTION

This invention relates to Streptococcal Hsp60 proteins, including 5 fragments thereof, and nucleic acid molecules encoding such proteins and fragments, in particular from *Streptococcus pneumoniae* and *Streptococcus pyogenes*, and uses of such proteins and nucleic acid molecules.

BACKGROUND OF THE INVENTION

10 The World Health Organization has estimated that, worldwide, about 30% of deaths of children under age 5, or about 4-5 million, result from acute respiratory infections. David Klein, *Pneumococcal Conjugate Vaccines: Review and Update*, in *Microbial Drug Resistance* 1:49, 1995. The most frequent causative agent responsible for these deaths is *Streptococcus pneumoniae*, which is also referred to as 15 pneumococcus and causes a wide variety of infections such as sinusitis, otitis, pneumonia, bacteremia and meningitis. This organism is found on respiratory mucosal membranes of 15-35% of healthy children and up to 80% of children with respiratory infections. Gray et al., *J. Infect. Dis.* 142:923, 1980; Hendley et al., *J. Infect. Dis.* 132:55, 1975. In addition, *Streptococcus pneumoniae* is responsible for 70,000 20 meningitis deaths and a similar number of deaths from sepsis and other infections.

In developing countries, Pneumococcal infections are responsible for approximately 1.2 million deaths among children 5 years of age and younger, which corresponds to nearly 40% of all pneumonia related deaths. World Health Organization, *Pneumococcal Conjugate Vaccines*, reported in Report of Meeting of 25 November 15-17, 1993 (WHO/ARI/94.34). In the industrialized world, taking the U.S. as an example, pneumococcus is a leading cause of severe morbidity in the general population and of death in the elderly as well as the immunocompromised population. Klein et al. (*supra*). Pneumococcus causes more deaths (about 50,000) in older adults 30 than any other infectious agent. High risk individuals include those with sickle cell anemia, nephrotic syndrome, asplenia, alcoholism and HIV infection. Pneumococcus

also poses a large risk to children under the age of two. In infants below the age of two, pneumococcus is the predominant cause of meningitis, bacteremia and otitis media. Within the first two years of life, about 25% of children experience otitis media caused by pneumococcus, a percentage that increases to 75% by the age of six. In Finland, 5 two-year old children have experienced, on average, more than one episode of otitis media. About half of the cases of acute otitis media were determined to be caused by pneumococcus. Eskola, J. and Kaeyhty, H., *Ann. Med.* 27:53, 1995.

Pneumococcus is a gram-positive organism that has type-specific capsular polysaccharides. Eighty-three different type specificities have been identified 10 and have been designated 1-83 in the American system. Jennings, *Current Topics in Microbiology and Immunology* 150:97-121, 1990. The structures of the different Pneumococcal polysaccharides have been reviewed by Kenne and Lindberg in *The Polysaccharides* 2:282-363 (Aspinal ed., 1983).

The need for an effective way to generate an immune response against 15 *Streptococcus pneumoniae* was recognized long ago. In 1945 it was demonstrated that isolated capsular polysaccharides were able to provide type-specific protection in humans. MacLeod et al., *J. Exp. Med.* 82:445-65, 1945. However, this protection was inadequate due to the large number of different polysaccharides needed for complete protection. The interest in a vaccine soon subsided due to the success of antibiotic 20 treatment of infections.

Recently the interest in the development of an effective vaccine has 25 renewed. One reason was that antibiotic treatment of infectious diseases caused by encapsulated bacteria such as pneumococcus did not always prevent morbidity and mortality. For an analogous example, cured *Hemophilus influenzae* meningitis was a major cause of acquired mental retardation. Sell et al., *Pediatrics* 49:206-11, 1972. Another important reason for the renewed interest in vaccine development was the appearance and rapid spread of antibiotic-resistant strains of pneumococcus. For example, in two hospitals in Paris, France, the frequency of resistant isolates from patients increased from 1.8% in 1987 to 17% in 1990. In Barcelona, Spain, the rate of 30 resistance increased from 4.3% in 1979 to 40% in 1990. See Lonks and Medeiros,

Antimicrobial Therapy 1 79:523-35, 1995. Multidrug-resistant pneumococcus have also appeared in many countries including 18 of the 50 states of the United States.

A vaccine containing polysaccharide antigens for 14 of the 83 capsular types was developed and released in 1978. Lonks and Medeiros, *supra*. This vaccine, 5 was improved in 1983 by the creation of second generation vaccine containing 23 different polysaccharides. However, two large studies, using this vaccine, one with 2837 patients, showed that the improved vaccine was only about 57% efficacious against Pneumococcal bacteremia. Butler et al., *JAMA* 270:1826, 1993.

A drawback to polysaccharide-based vaccines is that the efficacy of 10 these vaccines is problematic in infants under two years of age, who respond very poorly to these vaccines. Gotschlich et al., *Antibodies in Human Diagnosis and Therapy* 391-402 (Haber and Krause eds., 1977). An additional drawback is that antibodies produced by polysaccharide-based vaccines are predominantly of the IgM isotype, and therefore the immune response is not heightened upon secondary exposure 15 to the antigen.

These and other concerns about polysaccharide-based vaccines demonstrate that there is a need in the art for improved compositions which can be used to generate an immunogenic response directed to *Streptococcus pneumoniae*.

Turning to *Streptococcus pyogenes*, also referred to as group A 20 *streptococcus* ("GAS"), it too is a gram-positive bacterium that is causatively associated with a number of human disease states, ranging from acute pharyngitis (strep throat) to invasive diseases involving degeneration of the heart valves (acute rheumatic fever) and acute post-Streptococcal glomerulonephritis. Facklam, *Development of Group A Streptococcal Vaccines, in Manual of Clinical Microbiology* 1-22 (Lennette, Balows, 25 Hausler and Truant eds., 1980). Infection by this bacterium can also cause impetigo (a suppurative mucosal infection), invasive fasciitis (viz. flesh-eating disease), boils and skin abscesses (pyoderma), scarlet fever, sepsis, a severe toxic-shock like syndrome and pneumonia.

Before the advent of antibiotic therapy, rheumatic fever was a leading 30 cause of mortality in children and of chronic heart disease in individuals who survived

systemic infection. In developing countries, rheumatic fever is still an enormous problem. It has been estimated that in India over 6 million school age children suffer from rheumatic heart disease. Agarwal, *Lancet* 1 910-11, 1981. In the United States, the CDC has estimated that 25-40 million cases of *Streptococcus pyogenes*-induced pharyngitis occur every year, costing over \$2 billion for physician visits, culture work and antibiotic therapy. There also has been an increase in toxic-shock like syndrome caused by the organism. Presently, 10,000-15,000 cases of Streptococcal and Staphylococcal Toxic shock like infections occur annually in the United States. While presently GAS infections are treated with antibiotics, given what is known about other bacteria including pneumococcus (as detailed above), the proliferation of antibiotic-resistant strains is a concern.

GAS are differentiated from other streptococci by their Group A carbohydrate, a cell wall moiety containing rhamnose and N-acetyl glucosamine. Different strains of GAS are classified, serologically, based on their M protein or on the T antigen. GAS can be assigned to 80-100 different M protein groups which form the principal basis for characterizing pathological strains. The M protein is a surface protein and is both a major virulence factor and a major protective antigen. Lancefield, *J. Immunol.* 89:307, 1962. Antibodies against M protein are opsonic and promote killing of the bacteria by phagocytes. Lancefield, *supra*.

While M proteins are potentially useful in the constitution of a vaccine, several obstacles remain on the route to an effective vaccine. First, the M protein contains epitopes that cross-react with human tissue, especially the myocardium. Dale and Beachy, *J. Exp. Med.* 161:113, 1985. Thus, anti-M protein antibodies may cause disease rather than preventing it. Second, it may not be practical to produce a vaccine against all 80-100 different strains of GAS. Any vaccine containing only a few types of M protein may be only partially effective. While the first problem might be overcome by using M protein fragments that lack the cross-reactive epitopes as immunogens (Dale et al., *J. Immunol.* 151:2188-94, 1993), such an approach has not yet been proven, and the latter problem of immunizing against numerous distinct M proteins still needs to be overcome. Accordingly, there is a need in the art for a composition which provides



nucleotide bases of any one of SEQ ID NO:1 from nucleotides 15-1652, SEQ ID NO:3 from nucleotides 15-1640, SEQ ID NO:5 from nucleotides 15-1649, or SEQ ID NO:7 from nucleotides 15-1652 or a complement thereof or an isolated nucleic acid molecule encoding Hsp60 comprising a nucleic acid sequence that encodes a polypeptide 5 comprising any one of SEQ ID NOS: 2, 4, 6 or 8 or a variant Hsp60 that is at least 95% homologous to a polypeptide according to any one of SEQ ID NOS: 2, 4, 6 or 8.

In one embodiment, the present invention provides an isolated nucleic acid molecule according as described above, the molecule encoding a polypeptide that is able to be selectively bound by an antibody specific for a *Streptococcus pneumoniae* 10 Hsp60 or a *Streptococcus pyogenes* Hsp60.

In still another aspect in one aspect the present invention provides an isolated nucleic acid molecule encoding at least 8 amino acids of a Streptococcal Hsp60 polypeptide selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-541 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and 15 amino acid residues 1-545 of SEQ ID NO:8, wherein the encoded Streptococcal Hsp60 polypeptide is able to bind to a major histocompatibility complex.

In still further aspects the present invention provides an isolated *Streptococcus pneumoniae* Hsp60 polypeptide and an isolated *Streptococcus pyogenes* Hsp60 polypeptide.

20 In some embodiments, the isolated Hsp60 polypeptide comprises the amino acid sequence of any one of a Streptococcal Hsp60 polypeptide selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-541 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, or variants thereof, preferably wherein the polypeptide is able to be 25 selectively bound by an antibody specific for either a *Streptococcus pneumoniae* Hsp60 and/or *Streptococcus pyogenes* Hsp60. In further embodiments, the isolated Hsp60 polypeptide is fused to an additional polypeptide to create a fusion protein.

In still yet further aspects the present invention provides an isolated Hsp60 polypeptide comprising at least 8 amino acids selected from amino acid residues 30 1-545 of SEQ ID NO:2, amino acid residues 1-541 of SEQ ID NO:4, amino acid

residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, wherein the Hsp60 polypeptide is capable of binding to a major histocompatibility complex and eliciting or enhancing an immune response to *Streptococcus* in a human being.

5 In certain embodiments, the isolated Hsp60 polypeptide is derived from proteolytic cleavage or chemical synthesis, is an expression product of a transformed host cell containing a nucleic acid molecule encoding the Hsp60 or portion thereof. In further certain embodiments, the isolated Hsp60 polypeptide comprises greater than 95% homology to any one of a Streptococcal Hsp60 polypeptide selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-5410 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, and wherein the Hsp60 polypeptide is able to be selectively bound by an antibody specific for either a *Streptococcus pneumoniae* Hsp60 or *Streptococcus pyogenes* Hsp60 or both.

10 In still yet another aspect the present invention provides an isolated polypeptide wherein the polypeptide is an expression product of a transformed host cell containing one or more of the nucleic acid molecules described herein.

15 In still yet further aspects the present invention provides vectors comprising one or more of the nucleic acid molecules described herein. In certain embodiments, the vector is an expression vector comprising a promoter in operative linkage with the isolated nucleic acid molecule encoding the Hsp60 or portion thereof, preferably further comprising a selectable or identifiable marker and/or wherein the promoter is a constitutive or an inducible promoter. The present invention also provides host cells containing such vectors. In certain embodiments, the host cell is selected from the group consisting of a bacterial cell, a mammalian cell, a yeast cell and an insect cell.

20 In still yet other aspects the present invention provides compositions comprising an Hsp60 polypeptide as described herein in combination with a pharmaceutically acceptable carrier or diluent. In certain embodiments, the

composition is suitable for systemic administration, oral administration or parenteral administration.

In yet other aspects the present invention provides methods for eliciting or enhancing an immune response in a mammal against *Streptococcus*, comprising 5 administering to the mammal an effective amount of an Hsp60 polypeptide as described herein in combination with a pharmaceutically acceptable carrier or diluent, methods for eliciting or enhancing an immune response in a mammal against a target antigen comprising administering to the mammal the target antigen joined to an Hsp60 polypeptide as described herein in combination with a pharmaceutically acceptable 10 carrier or diluent.

In another aspect the present invention provides compositions comprising an isolated nucleic acid molecule as described herein wherein the isolated nucleic acid molecule encodes a polypeptide having at least one amino acid difference from a corresponding polypeptide of an Hsp60 protein from an organism other than 15 *Streptococcus*.

These and other aspects of the present invention will become evident upon reference to the present specification and the attached drawings. In addition, various references are set forth herein that describe in more detail certain procedures or compositions (e.g., plasmids, etc.); all such references are incorporated herein by 20 reference in their entirety.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the nucleotide and amino acid sequences of *Streptococcus pneumoniae* Hsp60-1 gene (SEQ ID NOS: 1 and 2 respectively).

25 Figure 2 depicts the nucleotide and amino acid sequences of *Streptococcus pneumoniae* Hsp60-2 gene (SEQ ID NOS: 3 and 4 respectively).

Figure 3 depicts the nucleotide and amino acid sequences of *Streptococcus pyogenes* Hsp60-1 gene (SEQ ID NOS: 5 and 6 respectively).

Figure 4 depicts the nucleotide and amino acid sequences of 30 *Streptococcus pyogenes* Hsp60-2 gene (SEQ ID NOS: 7 and 8 respectively).

Figure 5 is a schematic representation of the sequencing strategy used to deduce the sequences of the Hsp60 genes from *S. pneumoniae* and *S. pyogenes*.

Figures 6-9 depict maps of expression vectors pETP60-1, pETP60-2, pETY60-1, and pETY60-2, which vectors include the Hsp60 genes from *S. pneumoniae* or *S. pyogenes*, respectively.

Figure 10 depicts a comparison of the *S. pneumoniae* (SEQ ID NOS: 2 and 4) and *S. pyogenes* (SEQ ID NOS: 6 and 8) Hsp60 genes with similar genes from other organisms (SEQ ID NOS: 9 through 34).

Figure 11 depicts RP-HPLC chromatograms of the Hsp60 genes from *S. pneumoniae* and *S. pyogenes*.

DETAILED DESCRIPTION OF INVENTION

The present invention provides methods and compositions comprising isolated nucleic acid molecules and polypeptides specific to *Streptococcus pneumoniae* and *Streptococcus pyogenes*, as well as vector constructs, antibodies and other materials related to isolated nucleic acid molecules and polypeptides. Such compositions and methods are useful for the diagnosis of Streptococcal infection and for generating an immune response to Streptococcal bacteria.

A "stress gene," also known as "heat shock gene," is a gene that is activated or otherwise detectably upregulated due to the contact or exposure of an organism (containing the gene) to a stressor, such as heat shock or glucose deprivation or glucose addition. A given "stress gene" also includes homologous genes within known stress gene families, such as certain genes within the Hsp60, Hsp70 and Hsp90 stress gene families, even though such homologous genes are not themselves induced by a stressor. As defined herein, a "stress protein," also known as a "heat shock protein," ("Hsp") is a protein that is encoded by a stress gene, and is therefore typically produced in significantly greater amounts upon the contact or exposure to the stressor of the organism. Each of the terms stress gene and stress protein as used in the present specification are inclusive of the other, unless the context indicates otherwise. Streptococcal Hsps, as well as Hsps from other organisms, appear to participate in

important cellular processes such as protein synthesis and assembly and disassembly of protein complexes.

A variety of stress genes and proteins are well known in the art and include, for example, Hsp100-200, Hsp100, Hsp90, Lon, Hsp70, Hsp60, TF55, Hsp40, 5 FKBPs, cyclophilins, Hsp20-30, ClpP, GrpE, Hsp10, ubiquitin, calnexin, peptidyl-prolyl cis-trans isomerases, and protein disulfide isomerases. Macario, A.J.L., *Int. J. Clin. Lab. Res.* 25:59-70, 1995; Parsell, D.A., & Lindquist, S., *Ann. Rev. Genet.* 27: 437-496 (1993); U.S. Patent No. 5,232,833 (Sanders et al.).

In bacteria, the predominant stress proteins are proteins with molecular 10 sizes of about 60 and 70 kDa (*i.e.*, Hsp60 and Hsp70, respectively). Hsp70 and Hsp60 typically represent about 1-3% of bacterial cell protein based on the staining pattern using sodium dodecyl sulfate-polyacrylamide gel electrophoresis ("SDS-PAGE") and the stain coomassie blue, but accumulate to levels as high as 25% under stressful conditions. Thus, Hsps are produced in an invading bacterium due to stresses put on the 15 bacterium by the environment of the animal, and the Hsps become some of the most significant bacterial antigens displayed to the host and to which the host mounts an immune response. Therefore, by administering a Streptococcal Hsp to an animal, the Streptococcal Hsp can induce an immune response in the animal to *Streptococcus*, preferably providing resistance to such a bacterial infection. Accordingly, the isolation 20 of Streptococcal Hsp60 genes provides a platform for the generation of isolated polypeptides or fragments or variants of Streptococcal Hsp60 useful in diagnosis and inhibition of Streptococcal associated disorders.

As used herein, "polypeptide" refers to full length proteins and fragments thereof.

25 As used herein, "peptide" refers to a fragment of the whole protein, whether chemically or biologically produced.

As used herein, "immunogenic" refers to an antigen or composition that elicits an immune response.

An "isolated nucleic acid molecule" refers to a polynucleotide molecule, 30 in the form of a separate fragment or as a component of a larger nucleic acid construct,

that has been separated from its source cell (including the chromosome it normally resides in) at least once in a substantially pure form. Nucleic acid molecules can be comprised of a wide variety of nucleotides and molecules well known in the art, including DNA, RNA, nucleic acid analogues, or any combination of these.

5 As used herein, "vector" refers to a polynucleotide assembly capable of directing expression and/or replication of the nucleic acid sequence of interest. Such assembly can, if desired, be included as a part of other components, such as a protein, lipid or lipoprotein coat, for delivery of the vector or for other purposes.

10 An "expression vector" refers to polynucleotide vector having at least a promoter sequence operably linked to the nucleic acid sequence of interest.

15 As used herein, a "promoter" refers to a nucleotide sequence that contains elements that direct the transcription of an operably linked nucleic acid sequence. At minimum, a promoter contains an RNA polymerase binding site. Promoter regions can also contain enhancer elements which by definition enhance transcription.

A. HSP60 GENES AND POLYPEPTIDES FROM *STREPTOCOCCUS PNEUMONIAE* AND *STREPTOCOCCUS PYOGENES*

As used herein, Hsp60 refers to heat shock genes from the Hsp60 family of genes that produce heat shock proteins of approximately 60kDa; the nucleotide and amino acid sequences of Hsp60 genes and gene products from *Streptococcus pneumoniae* and *Streptococcus pyogenes* are set forth in Figures 1-4 (SEQ ID NOS:1-8; such sequences also include the PCR primers used to isolate the Hsp60 genes). Within the context of this invention it should be understood that Hsp60 includes wild-type/native protein sequences, as well as other variants (including alleles) and fragments of the native protein sequence. Briefly, such variants may result from natural polymorphisms or be synthesized by recombinant methodology or chemical synthesis, and differ from wild-type proteins by one or more amino acid substitutions, insertions, deletions, or the like. Further, in the region of homology to the native sequence, variants should preferably have at least 95% amino acid sequence homology, and within

certain embodiments, greater than 97% or 98% homology. As will be appreciated by those of ordinary skill in the art, a nucleotide sequence encoding Hsp60 or variant may differ from the native sequences presented herein due to codon degeneracies, nucleotide polymorphisms, or nucleotide substitutions, deletions or insertions.

5 An "isolated nucleic acid molecule encoding *Streptococcus* Hsp60" refers to nucleic acid sequences that are capable of encoding Hsp60 polypeptides of *Streptococcus*, preferably *Streptococcus pneumoniae* or *Streptococcus pyogenes*. While several embodiments of such molecules are depicted in SEQ ID NOS:1-4, it should be understood that within the context of the present invention, reference to one or more of
10 these genes includes variants of the genes, that is, naturally occurring variants or sequences that are substantially similar to the genes (and, where appropriate, the protein (including peptides and polypeptides) that are encoded by the genes and their variants). As used herein, the nucleotide sequence is deemed to be "substantially similar" if: (a) the nucleotide sequence is derived from the coding region of a native gene of
15 *Streptococcus* and maintains substantially the same biological activity (including, for example, portions of the sequence or allelic variations of the sequences discussed above); or (b) the nucleotide sequence is capable of hybridization to the nucleotide sequences of the present invention under high stringency (*i.e.*, capable of selectively hybridizing to nucleotide sequences from *Streptococcus*); or (c) the nucleotide
20 sequences are degenerate (*i.e.*, sequences which code for the same amino acid using a different codon sequence) as a result of the genetic code to the nucleotide sequences defined in (a) or (b); or (d) is a complement of any of the sequences described in (a), (b) or (c)

One aspect of the present invention is the use of *Streptococcus* Hsp60
25 nucleotide sequences to produce recombinant proteins for immunizing an animal. Therefore, the use of any length of nucleic acid disclosed by the present invention (preferably 24 nucleotides or longer) which encodes a polypeptide or fragment thereof that is capable of binding to the major histocompatibility complex and eliciting or enhancing an immunogenic response is contemplated by this invention. Immunogenic
30 response can be readily tested by known methods such as challenging a mouse or rabbit

with the antigen of interest and thereafter collecting plasma and determining if the antibody of interest is present. Other assays particularly useful for the detection of T-cell responses include proliferation assays, T-cell cytotoxicity assays and assays for delayed hypersensitivity. In determining whether an antibody specific for the antigen of interest was produced by the animal, many diagnostic tools are available, for example, testing binding of labeled antigen to plasma derived antibodies, or using Enzyme-linked immunoassays with tag attached to the antigen of interest.

The Streptococcal Hsp60 genes of this invention can be obtained using a variety of methods. For example, a nucleic acid molecule can be obtained from a 10 cDNA or genomic expression library by screening with an antibody or antibodies reactive to one or more of these Hsp60s (see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor, 1989; Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing, 1987). Further, random-primed PCR can be employed (see, e.g., *Methods in Enzymol.* 254:275, 1995). In addition, variations of 15 random-primed PCR can also be used, especially when a particular gene or gene family is desired. In one such method, one of the primers is a poly deoxy-thymine and the other is a degenerate primer based on the amino acid sequence or nucleotide sequence of related Hsps.

Other methods can also be used to obtain a nucleic acid molecule that 20 encodes Streptococcal Hsp60. For example, a nucleic acid molecule can be obtained by using the sequence information provided herein to synthesize a probe which can be labeled, such as with a radioactive label, enzymatic label, protein label, fluorescent label, or the like, and hybridized to a genomic library or a cDNA library constructed in a phage, plasmid, phagemid, or other viral vector (see, e.g., Sambrook et al. (*supra*); 25 Ausubel et al. (*supra*)). DNA representing RNA or genomic nucleic acid sequence can also be obtained by amplification using sets of primers complementary to 5' and 3' sequences of the cDNA sequence, such as presented in Example 1. For ease of cloning, restriction sites can also be incorporated into the primers.

Variants (including alleles) of the Hsp60 genes provided herein can be 30 readily isolated from natural variants (e.g., polymorphisms, mutants), synthesized or

constructed. Many methods have been developed for generating mutants (*see generally* Sambrook et al. (*supra*); Ausubel et al. (*supra*)). Briefly, preferred methods for generating nucleotide substitutions utilize an oligonucleotide that spans the base or bases to be mutated and contains the mutated base or bases. The oligonucleotide is 5 hybridized to complementary single stranded nucleic acid and second strand synthesis is primed from the oligonucleotide. The double-stranded nucleic acid is prepared for transformation into host cells, such as *E. coli*, other prokaryotes, yeast or other eukaryotes. Standard screening and vector growth protocols are used to identify mutant sequences and obtain high yields.

10 Similarly, deletions and/or insertions of the Hsp60 gene can be constructed by any of a variety of known methods. For example, the gene can be digested with restriction enzymes and religated such that sequence is deleted or religated with additional sequence such that an insertion or large substitution is made. Other means of generating variant sequences, known in the art, can be employed, for 15 examples see Sambrook et al. (*supra*) and Ausubel et al. (*supra*). Moreover, verification of variant sequences is typically accomplished by restriction enzyme mapping, sequence analysis or hybridization. Variants which encode a polypeptide that elicits an immunogenic response specific for *Streptococcus* are useful in the context of this invention.

20 As noted above, the present invention also provides isolated polypeptides. Within the context of the present invention, unless otherwise clear from the context, such polypeptides are understood to include the whole, or portions/fragments, of a gene product derived from one or more of the Streptococcal Hsp60 genes or derivatives thereof as discussed above. In one aspect of the present invention, the protein is encoded by a portion of a native gene or is encoded by a derivative of a native gene and the protein or fragment thereof elicits or enhances an immune response specific for *Streptococcus*.

25 A "purified" Hsp60 stress protein of the present invention is a heat shock protein of the Hsp60 family from *Streptococcus pneumoniae* or *Streptococcus pyogenes* 30 that has been purified from its producing cell. For example, the Streptococcal Hsp60

polypeptides of the present invention can be purified by a variety of standard methods with or without a detergent purification step. For example, Streptococcal Hsp60 can be isolated by, among other methods, culturing suitable host and vector systems to produce recombinant Hsp60 (discussed further herein). Then, supernatants from such cell lines, 5 or Hsp60 inclusions, or whole cells where the Hsp60 is not excreted into the supernatant, can be treated by a variety of purification procedures. For example, the Streptococcal Hsp60-containing composition can be applied to a suitable purification matrix such as an anti-Hsp60 antibody bound to a suitable support. Alternatively, anion or cation exchange resins, gel filtration or affinity, hydrophobic or reverse phase 10 chromatography may be employed in order to purify the protein. The Hsp60 polypeptide can also be concentrated using commercially available protein concentration filters, such as an Amicon or Millipore Pellicon ultrafiltration unit, or by vacuum dialysis. In another alternative the supernatant can first be concentrated using one of the above mentioned protein concentration filters, followed by application of the 15 concentrate to a suitable purification matrix such as those described above.

In one embodiment, the isolated Streptococcal Hsp60s of the present invention are produced in a recombinant form, utilizing genetic manipulation techniques that are well known in the art. For example, Streptococcal Hsp60 can be expressed as a histidine-tagged molecule, permitting purification on a nickel-chelating 20 matrix. Alternatively, other tags may be used, including FLAG and GST. The associated tag can then be removed in the last step of purification, for example, for certain vectors, His-tagged proteins may be incubated with thrombin, resulting in cleavage of a recognition sequence between the tag and the Hsp60 polypeptide (e.g., pET vectors from Invitrogen). Following purification of Streptococcal Hsp60 from a 25 gram-negative bacterial host, whether tagged or not, it will be necessary to reduce the level of endotoxin in the Hsp60 preparation, as discussed above.

B. VECTORS, HOST CELLS, AND EXPRESSION OF STREPTOCOCCAL HSP60

It is well known in the art that certain vectors (e.g., pUC) can be used for 30 producing multiple copies of a nucleotide molecule of interest as well as being useful

for genetic manipulation techniques (e.g., site-directed mutagenesis). See Sambrook (*supra*). Of particular interest to this disclosure are expression vectors. The expression vector includes transcriptional promoter/enhancer elements operably linked to the Streptococcal Hsp60 nucleic acid molecule. The expression vector may be composed of 5 either deoxyribonucleic acids ("DNA"), ribonucleic acids ("RNA"), or a combination of the two (e.g., a DNA-RNA chimera). Optionally, the expression vector may include a polyadenylation sequence or one or more restriction sites. Additionally, depending on the host cell chosen and the expression vector employed, other genetic elements such as an origin of replication, additional nucleic acid restriction sites, enhancers, sequences 10 conferring inducibility of transcription, and genes encoding proteins suitable for use as selectable or identifiable markers, may also be incorporated into the expression vectors described herein.

The manipulation and expression of Streptococcal Hsp60 genes can be accomplished by culturing host cells containing an expression vector capable of 15 expressing the Hsp60 genes. Such vectors or vector constructs include either synthetic or cDNA-derived nucleic acid molecules or genomic DNA fragments encoding Streptococcal Hsp60 polypeptides, which are operably linked to suitable transcriptional or translational regulatory elements. Suitable regulatory elements within the expression vector can be derived from a variety of sources, including bacterial, fungal, viral, 20 mammalian, insect, or plant genes. Selection of appropriate regulatory elements is dependent on the host cell chosen, and can be readily accomplished by one of ordinary skill in the art in light of the present specification. Examples of regulatory elements include a transcriptional promoter and enhancer or RNA polymerase binding sequence, a transcriptional terminator, and a ribosomal binding sequence, including a translation 25 initiation signal.

Nucleic acid molecules that encode any of the Streptococcal Hsp60 polypeptides described above can be expressed by a wide variety of prokaryotic and eukaryotic host cells, including bacterial, mammalian, yeast or other fungi, viral, insect, and plant cells. The selection of a host cell may also assist the production of 30 glycosolated or non-glycosolated Hsp60s, depending upon the desires of the user.

Methods for transforming or transfecting such cells to express nucleic acids are well known in the art (see, e.g., Itakura et al., U.S. Patent No. 4,704,362; Hinnen et al., *PNAS USA* 75:1929-1933, 1978; Murray et al., U.S. Patent No. 4,801,542; Upshall et al., U.S. Patent No. 4,935,349; Hagen et al., U.S. Patent No. 4,784,950; Axel et al., U.S. 5 Patent No. 4,399,216; Goeddel et al., U.S. Patent No. 4,766,075; and Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd edition, Cold Spring Harbor Laboratory Press, 1989; for plant cells see Czako and Marton, *Plant Physiol.* 104:1067-1071, 1994; Paszkowski et al., *Biotech.* 24:387-392, 1992).

Bacterial host cells suitable for carrying out the present invention include 10 *E. coli*, such as *E. coli* DH5 α (Stratagene, La Jolla, California), *M. leprae*, *M. tuberculosis*, *M. bovis*, *B. subtilis*, *Salmonella typhimurium*, and various species within the genera *Pseudomonas*, *Streptomyces*, *Streptococcus*, and *Staphylococcus*, as well as many other bacterial species well known to one of ordinary skill in the art.

Bacterial expression vectors preferably comprise a promoter, which 15 functions in the host cell, one or more selectable phenotypic markers, and a bacterial origin of replication. Representative promoters include the β -lactamase (penicillinase) and lactose promoter system (see Chang et al., *Nature* 275:615, 1978), the T7 RNA polymerase promoter (Studier et al., *Meth. Enzymol.* 185:60-89, 1990), the lambda promoter (Elvin et al., *Gene* 87:123-126, 1990), the *trp* promoter (Nichols and 20 Yanofsky, *Meth. in Enzymology* 101:155, 1983) and the *tac* promoter (Russell et al., *Gene* 20: 231, 1982). Representative selectable markers include various antibiotic 25 resistance markers such as the kanamycin or ampicillin resistance genes. Many plasmids suitable for transforming host cells are well known in the art, including among others, pBR322 (see Bolivar et al., *Gene* 2:95, 1977), the pUC plasmids pUC18, pUC19, pUC118, pUC119 (see Messing, *Meth. in Enzymology* 101:20-77, 1983; Vieira and Messing, *Gene* 19:259-268, 1982), and pNH8A, pNH16a, pNH18a, and Bluescript M13 (Stratagene, La Jolla, Calif.).

Fungal host cells suitable for carrying out the present invention include, among others, *Saccharomyces pombe*, *Saccharomyces cerevisiae*, the genera *Pichia* or 30 *Kluyveromyces* and various species of the genus *Aspergillus* (McKnight et al., U.S.

Patent No. 4,935,349). Suitable expression vectors for yeast and fungi include, among others, YCp50 (ATCC No. 37419) for yeast, and the *amdS* cloning vector pV3 (Turnbull, *Bio/Technology* 7:169, 1989), YRp7 (Struhl et al., *Proc. Natl. Acad. Sci. USA* 76:1035-1039, 1978), YEp13 (Broach et al., *Gene* 8:121-133, 1979), pJDB249 and 5 pJDB219 (Beggs, *Nature* 275:104-108, 1978) and derivatives thereof.

Preferred promoters for use in yeast include promoters from yeast glycolytic genes (Hitzeman et al., *J. Biol. Chem.* 255:12073-12080, 1980; Alber and Kawasaki, *J. Mol. Appl. Genet.* 1:419-434, 1982) or alcohol dehydrogenase genes (Young et al., in *Genetic Engineering of Microorganisms for Chemicals*, Hollaender et 10 al. (eds.), p. 355, Plenum, New York, 1982; Ammerer, *Meth. Enzymol.* 101:192-201, 1983). Examples of useful promoters for fungi vectors include those derived from *Aspergillus nidulans* glycolytic genes, such as the *adh3* promoter (McKnight et al., *EMBO J.* 4:2093-2099, 1985). The expression units may also include a transcriptional terminator. An example of a suitable terminator is the *adh3* terminator (McKnight et 15 al., *ibid.*, 1985).

As with bacterial vectors, the yeast vectors will generally include a selectable marker, which may be one of any number of genes that exhibit a dominant phenotype for which a phenotypic assay exists to enable transformants to be selected. Preferred selectable markers include those that complement host cell auxotrophy, 20 provide antibiotic resistance or enable a cell to utilize specific carbon sources, and include *leu2* (Broach et al., *ibid.*), *ura3* (Botstein et al., *Gene* 8:17, 1979), or *his3* (Struhl et al., *ibid.*). Another suitable selectable marker is the *cat* gene, which confers chloramphenicol resistance on yeast cells.

Techniques for transforming fungi are well known in the literature, and 25 have been described, for instance, by Beggs (*ibid.*), Hinnen et al. (*Proc. Natl. Acad. Sci. USA* 75:1929-1933, 1978), Yelton et al. (*Proc. Natl. Acad. Sci. USA* 81:1740-1747, 1984), and Russell (*Nature* 301:167-169, 1983). The genotype of the host cell may contain a genetic defect that is complemented by the selectable marker present on the expression vector. Choice of a particular host and selectable marker is well within the 30 level of ordinary skill in the art in light of the present specification.

Protocols for the transformation of yeast are also well known to those of ordinary skill in the art. For example, transformation may be readily accomplished either by preparation of spheroplasts of yeast with DNA (see Hinnen et al., *PNAS USA* 75:1929, 1978) or by treatment with alkaline salts such as LiCl (see Itoh et al., *J. Bacteriology* 153:163, 1983). Transformation of fungi may also be carried out using 5 polyethylene glycol as described by Cullen et al. (*Bio/Technology* 5:369, 1987).

Viral vectors include those that comprise a promoter that directs the expression of an isolated nucleic acid molecule that encodes a Streptococcal Hsp60 as described above. A wide variety of promoters may be utilized within the context of the 10 present invention, including for example, promoters such as MoMLV LTR, RSV LTR, Friend MuLV LTR, adenoviral promoter (Ohno et al., *Science* 265: 781-784, 1994), neomycin phosphotransferase promoter/enhancer, late parvovirus promoter (Koering et al., *Hum. Gene Therap.* 5:457-463, 1994), Herpes TK promoter, SV40 promoter, metallothionein IIa gene enhancer/promoter, cytomegalovirus immediate early 15 promoter, and the cytomegalovirus immediate late promoter. The promoter may also be a tissue-specific promoter (see e.g., WO 91/02805; EP 0,415,731; and WO 90/07936). In addition to the above-noted promoters, other viral-specific promoters (e.g., retroviral 20 promoters (including those noted above, as well as others such as HIV promoters), hepatitis, herpes (e.g., EBV), and bacterial, fungal or parasitic-specific (e.g., malarial-specific) promoters may be utilized in order to target a specific cell or tissue which is infected with a virus, bacteria, fungus or parasite.

Thus, Streptococcal Hsp60 polypeptides of the present invention may be expressed from a variety of viral vectors, including for example, herpes viral vectors (e.g., U.S. Patent No. 5,288,641), adenoviral vectors (e.g., WO 94/26914, WO 93/9191; 25 Kolls et al., *PNAS* 91(1):215-219, 1994; Kass-Eisler et al., *PNAS* 90(24):11498-502, 1993; Guzman et al., *Circulation* 88(6):2838-48, 1993; Guzman et al., *Cir. Res.* 73(6):1202-1207, 1993; Zabner et al., *Cell* 75(2):207-216, 1993; Li et al., *Hum Gene Ther.* 4(4):403-409, 1993; Caillaud et al., *Eur. J. Neurosci.* 5(10):1287-1291, 1993; Vincent et al., *Nat. Genet.* 5(2):130-134, 1993; Jaffe et al., *Nat. Genet.* 1(5):372-378, 30 1992; and Levrero et al., *Gene* 101(2):195-202, 1991), adenovirus-associated viral

vectors (Flotte et al., *PNAS* 90(22):10613-10617, 1993), baculovirus vectors, parvovirus vectors (Koering et al., *Hum. Gene Therap.* 5:457-463, 1994), pox virus vectors (Panicali and Paoletti, *PNAS* 79:4927-4931, 1982; and Ozaki et al., *Biochem. Biophys. Res. Comm.* 193(2):653-660, 1993), and retroviruses (e.g., EP 0,415,731; WO 5 90/07936; WO 91/0285, WO 94/03622; WO 93/25698; WO 93/25234; U.S. Patent No. 5,219,740; WO 93/11230; WO 93/10218. Within various embodiments, either the viral vector itself or a viral particle which contains the viral vector may be utilized in the methods and compositions described below.

Mammalian cells suitable for carrying out the present invention include, 10 among others: PC12 (ATCC No. CRL1721), N1E-115 neuroblastoma, SK-N-BE(2)C neuroblastoma, SHSY5 adrenergic neuroblastoma, NS20Y and NG108-15 murine cholinergic cell lines, or rat F2 dorsal root ganglion line, COS (e.g., ATCC No. CRL 1650 or 1651), BHK (e.g., ATCC No. CRL 6281; BHK 570 cell line (deposited with the American Type Culture Collection under accession number CRL 10314), CHO 15 (ATCC No. CCL 61), HeLa (e.g., ATCC No. CCL 2), 293 (ATCC No. 1573; Graham et al., *J. Gen. Virol.* 36:59-72, 1977) and NS-1 cells. Other mammalian cell lines may be used within the present invention, including Rat Hep I (ATCC No. CRL 1600), Rat Hep II (ATCC No. CRL 1548), TCMK (ATCC No. CCL 139), Human lung (ATCC No. CCL 75.1), Human hepatoma (ATCC No. HTB-52), Hep G2 (ATCC No. HB 8065), 20 Mouse liver (ATCC No. CCL 29.1), NCTC 1469 (ATCC No. CCL 9.1), SP2/0-Ag14 (ATCC No. 1581), HIT-T15 (ATCC No. CRL 1777), and RINm 5AHT2B (Orskov and Nielson, *FEBS* 229(1):175-178, 1988).

Mammalian expression vectors for use in carrying out the present invention include a promoter capable of directing the transcription of a cloned gene or 25 cDNA. Preferred promoters include viral promoters and cellular promoters. Viral promoters include the cytomegalovirus immediate early promoter (Boshart et al., *Cell* 41:521-530, 1985), cytomegalovirus immediate late promoter, SV40 promoter (Subramani et al., *Mol. Cell. Biol.* 1:854-864, 1981), MMTV LTR, RSV LTR, metallothionein-1, adenovirus E1a. Cellular promoters include the mouse 30 metallothionein-1 promoter (Palmiter et al., U.S. Patent No. 4,579,821), action

promoters, a mouse V_H promoter (Bergman et al., *Proc. Natl. Acad. Sci. USA* 81:7041-7045, 1983; Grant et al., *Nucl. Acids Res.* 15:5496, 1987) and a mouse V_H promoter (Loh et al., *Cell* 33:85-93, 1983). The choice of promoter will depend, at least in part, upon the level of expression desired or the recipient cell line to be transfected.

5 Such expression vectors can also contain a set of RNA splice sites located downstream from the promoter and upstream from the DNA sequence encoding the peptide or protein of interest. Preferred RNA splice sites may be obtained from adenovirus and/or immunoglobulin genes. Also contained in the expression vectors is a polyadenylation signal located downstream of the coding sequence of interest. Suitable
10 polyadenylation signals include the early or late polyadenylation signals from SV40 (Kaufman and Sharp, *ibid.*), the polyadenylation signal from the Adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto et al., *Nuc. Acids Res.* 9:3719-3730, 1981). The expression vectors may include a noncoding viral leader sequence, such as the Adenovirus 2 tripartite leader, located between the promoter and
15 the RNA splice sites. Preferred vectors may also include enhancer sequences, such as the SV40 enhancer. Expression vectors may also include sequences encoding the adenovirus VA RNAs. Suitable expression vectors can be obtained from commercial sources (e.g., Stratagene, La Jolla, Calif.).

20 Vector constructs comprising cloned DNA sequences can be introduced into cultured mammalian cells by, for example, calcium phosphate-mediated transfection (Wigler et al., *Cell* 14:725, 1978; Corsaro and Pearson, *Somatic Cell Genetics* 7:603, 1981; Graham and Van der Eb, *Virology* 52:456, 1973), electroporation (Neumann et al., *EMBO J.* 1:841-845, 1982), or DEAE-dextran mediated transfection (Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc., NY, 1987). See generally Sambrook et al. (supra). To identify cells that have
25 stably integrated the cloned DNA, a selectable marker is generally introduced into the cells along with the gene or cDNA of interest. Preferred selectable markers for use in cultured mammalian cells include genes that confer resistance to drugs, such as neomycin, hygromycin, and methotrexate. The selectable marker may be an
30 amplifiable selectable marker. Preferred amplifiable selectable markers are the DHFR

gene and the neomycin resistance gene. Selectable markers are reviewed by Thilly (*Mammalian Cell Technology*, Butterworth Publishers, Stoneham, MA).

Mammalian cells containing a suitable vector are allowed to grow for a period of time, typically 1-2 days, to begin expressing the DNA sequence(s) of interest.

5 Drug selection is then applied to select for growth of cells that are expressing the selectable marker in a stable fashion. For cells that have been transfected with an amplifiable, selectable marker the drug concentration may be increased in a stepwise manner to select for increased copy number of the cloned sequences, thereby increasing expression levels. Cells expressing the introduced sequences are selected and screened

10 for production of the protein of interest in the desired form or at the desired level. Cells that satisfy these criteria can then be cloned and scaled up for production.

Numerous insect host cells known in the art can also be useful within the present invention, in light of the subject specification. For example, the use of baculoviruses as vectors for expressing heterologous DNA sequences in insect cells has

15 been reviewed by Atkinson et al. (*Pestic. Sci.* 28:215-224, 1990).

Numerous plant host cells known in the art can also be useful within the present invention, in light of the subject specification. For example, the use of *Agrobacterium rhizogenes* as vectors for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci. (Bangalore)* 11:47-58, 1987.

20 Upon expression of the Streptococcal Hsp60 polypeptides or fragments thereof in the host cells, the polypeptide or peptide may be preliminarily released and/or isolated from the host cell utilizing methods such as those discussed previously herein.

As noted above, depending on the host cell in which one desires to express Hsp60, the gene encoding the protein is introduced into an expression vector

25 comprising a promoter that is active in the host cell. Other components of the expression unit such as transcribed but not translated sequences at the ends of the coding region may also be selected according to the particular host utilized. In some cases, it may be necessary to introduce artificially an intervening sequence to ensure high level expression. Expression can be monitored by SDS-PAGE and staining, if

30 expression levels are sufficiently high. Additionally, if the protein is produced with a

tag, detection by anti-tag antibody can be carried out and if produced with no tag, detection by anti-Hsp60 antibody that does not recognize homologous proteins of the host may be employed. Further, any method known in the art for protein identification may be utilized to this end (e.g., a high resolution electrophoretic method or 2D 5 electrophoresis).

C. PREPARATION OF ANTIBODIES AGAINST THE HSP60 POLYPEPTIDES OF THE PRESENT INVENTION

In another aspect, the proteins of the present invention are utilized to 10 prepare specifically binding antibodies (*i.e.*, binding partners). Accordingly, the present invention also provides such antibodies. Within the context of the present invention, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, anti-idiotypic antibodies, fragments thereof such as F(ab')₂ and Fab fragments, and recombinantly or synthetically produced binding partners. Such binding partners 15 incorporate the variable regions that permit a monoclonal antibody to specifically bind, which means an antibody able to selectively bind to a peptide produced from one of the Streptococcal Hsp60 genes of the invention. The affinity of a monoclonal antibody or binding partner can be readily determined by one of ordinary skill in the art (*see* Scatchard, *Ann. N.Y. Acad. Sci.* 51:660-672, 1949).

20 Polyclonal antibodies can be readily generated by one of ordinary skill in the art from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, turkeys, rabbits, mice, or rats. Briefly, the desired protein or peptide is utilized to immunize the animal through intraperitoneal, intramuscular, intraocular, or subcutaneous injections. The immunogenicity of the protein or peptide of interest may 25 be increased through the use of an adjuvant such as Freund's complete or incomplete adjuvant. Following several booster immunizations, small samples of serum are collected and tested for reactivity to the desired protein or peptide.

Particularly preferred polyclonal antisera give a signal that is at least three times greater than background. Once the titer of the animal has reached a plateau

in terms of its reactivity to the protein, larger quantities of polyclonal antisera may be readily obtained either by weekly bleedings, or by exsanguinating the animal.

Monoclonal antibodies can also be readily generated using well-known techniques (see U.S. Patent Nos. RE 32,011, 4,902,614, 4,543,439, and 4,411,993; see 5 also *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Plenum Press, Kennett, McKearn, and Bechtol (eds.), 1980, and *Antibodies: A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988). Briefly, in one embodiment, a subject animal such as a rat or mouse is injected 10 with a desired protein or peptide. If desired, various techniques may be utilized in order to increase the resultant immune response generated by the protein, in order to develop greater antibody reactivity. For example, the desired protein or peptide may be coupled 15 to another protein such as ovalbumin or keyhole limpet hemocyanin (KLH), or through the use of adjuvants such as Freund's complete or incomplete adjuvant. The initial elicitation of an immune response, may preferably be through intraperitoneal, intramuscular, intraocular, or subcutaneous routes.

Between one and three weeks after the initial immunization, the animal may be reimmunized. The animal may then be test bled and the serum tested for binding to the desired antigen using assays as described above. Additional immunizations may also be accomplished until the animal has reached a plateau in its 20 reactivity to the desired protein or peptide. The animal may then be given a final boost of the desired protein or peptide, and three to four days later sacrificed. At this time, the spleen and lymph nodes may be harvested and disrupted into a single cell suspension by passing the organs through a mesh screen or by rupturing the spleen or lymph node membranes which encapsulate the cells. Within one embodiment the red cells are 25 subsequently lysed by the addition of a hypotonic solution, followed by immediate return to isotonicity.

Within another embodiment, suitable cells for preparing monoclonal antibodies are obtained through the use of *in vitro* immunization techniques. Briefly, an animal is sacrificed, and the spleen and lymph node cells are removed as described 30 above. A single cell suspension is prepared, and the cells are placed into a culture

containing a form of the protein or peptide of interest that is suitable for generating an immune response as described above. Subsequently, the lymphocytes are harvested and fused as described below.

Cells that are obtained through the use of *in vitro* immunization or from an immunized animal as described above may be immortalized by transfection with a virus such as the Epstein-Barr Virus (EBV). (See Glasky and Reading, *Hybridoma* 8(4):377-389, 1989.) Alternatively, within a preferred embodiment, the harvested spleen and/or lymph node cell suspensions are fused with a suitable myeloma cell in order to create a "hybridoma" which secretes monoclonal antibodies. Suitable myeloma lines are preferably defective in the construction or expression of antibodies, and are additionally syngeneic with the cells from the immunized animal. Many such myeloma cell lines are well known in the art and may be obtained from sources such as the American Type Culture Collection (ATCC), Rockville, Maryland (see *Catalogue of Cell Lines & Hybridomas*, 6th ed., ATCC, 1988). Representative myeloma lines include: for humans, UC 729-6 (ATCC No. CRL 8061), MC/CAR-Z2 (ATCC No. CRL 8147), and SKO-007 (ATCC No. CRL 8033); for mice, SP2/0-Ag14 (ATCC No. CRL 1581), and P3X63Ag8 (ATCC No. TIB 9); and for rats, Y3-Ag1.2.3 (ATCC No. CRL 1631), and YB2/0 (ATCC No. CRL 1662). Particularly preferred fusion lines include NS-1 (ATCC No. TIB 18) and P3X63 - Ag 8.653 (ATCC No. CRL 1580), which may be utilized for fusions with either mouse, rat, or human cell lines. Fusion between the myeloma cell line and the cells from the immunized animal can be accomplished by a variety of methods, including the use of polyethylene glycol (PEG) (see *Antibodies: A Laboratory Manual*, Harlow and Lane, *supra*) or electrofusion. (See Zimmerman and Vienken, *J. Membrane Biol.* 67:165-182, 1982.)

Following the fusion, the cells are placed into culture plates containing a suitable medium, such as RPMI 1640 or DMEM (Dulbecco's Modified Eagles Medium, JRH Biosciences, Lenexa, Kan.). The medium may also contain additional ingredients, such as Fetal Bovine Serum (FBS, e.g., from Hyclone, Logan, Utah, or JRH Biosciences), thymocytes that were harvested from a baby animal of the same species as was used for immunization, or agar to solidify the medium. Additionally, the medium

should contain a reagent which selectively allows for the growth of fused spleen and myeloma cells. Particularly preferred is the use of HAT medium (hypoxanthine, aminopterin, and thymidine) (Sigma Chemical Co., St. Louis, Mo.). After about seven days, the resulting fused cells or hybridomas may be screened in order to determine the presence of antibodies which recognize the desired antigen. Following several clonal dilutions and reassays, hybridoma producing antibodies that bind to the protein of interest can be isolated.

Other techniques may also be utilized to construct monoclonal antibodies. (See Huse et al., "Generation of a Large Combinational Library of the Immunoglobulin Repertoire in Phage Lambda," *Science* 246:1275-1281, 1989; see also Sastry et al., "Cloning of the Immunological Repertoire in *Escherichia coli* for Generation of Monoclonal Catalytic Antibodies: Construction of a Heavy Chain Variable Region-Specific cDNA Library," *Proc. Natl. Acad. Sci. USA* 86:5728-5732, 1989; see also Alting-Mees et al., "Monoclonal Antibody Expression Libraries: A Rapid Alternative to Hybridomas," *Strategies in Molecular Biology* 3:1-9, 1990; these references describe a commercial system available from Stratagene, La Jolla, California, which enables the production of antibodies through recombinant techniques.) Briefly, mRNA is isolated from a B cell population and utilized to create heavy and light chain immunoglobulin cDNA expression libraries in the λ IMMUNOZAP(H) and λ IMMUNOZAP(L) vectors. These vectors may be screened individually or co-expressed to form Fab fragments or antibodies (see Huse et al. (*supra*); see also Sastry et al. (*supra*)). Positive plaques can subsequently be converted to a non-lytic plasmid which allows high level expression of monoclonal antibody fragments from *E. coli*.

Similarly, binding partners can also be constructed utilizing recombinant DNA techniques to incorporate the variable regions of a gene that encodes a specifically binding antibody. The construction of these binding partners can be readily accomplished by one of ordinary skill in the art given the disclosure provided herein. (See Larrick et al., "Polymerase Chain Reaction Using Mixed Primers: Cloning of Human Monoclonal Antibody Variable Region Genes From Single Hybridoma Cells,"

Biotechnology 7:934-938, 1989; Riechmann et al., "Reshaping Human Antibodies for Therapy," *Nature* 332:323-327, 1988; Roberts et al., "Generation of an Antibody with Enhanced Affinity and Specificity for its Antigen by Protein Engineering," *Nature* 328:731-734, 1987; Verhoeyen et al., "Reshaping Human Antibodies: Grafting an 5 Antilysozyme Activity," *Science* 239:1534-1536, 1988; Chaudhary et al., "A Recombinant Immunotoxin Consisting of Two Antibody Variable Domains Fused to *Pseudomonas* Exotoxin," *Nature* 339:394-397, 1989; *see also* U.S. Patent No. 5,132,405 entitled "Biosynthetic Antibody Binding Sites.") Briefly, in one embodiment, DNA segments encoding the desired protein or peptide of interest-specific 10 antigen binding domains are amplified from hybridomas that produce a specifically binding monoclonal antibody, and are inserted directly into the genome of a cell that produces human antibodies. (*See* Verhoeyen et al. (*supra*); *see also* Reichmann et al. (*supra*)). This technique allows the antigen-binding site of a specifically binding mouse or rat monoclonal antibody to be transferred into a human antibody. Such antibodies 15 are preferable for therapeutic use in humans because they are not as antigenic as rat or mouse antibodies.

In an alternative embodiment, genes that encode the variable region from a hybridoma producing a monoclonal antibody of interest are amplified using oligonucleotide primers for the variable region. These primers may be synthesized by 20 one of ordinary skill in the art, or may be purchased from commercially available sources. For instance, primers for mouse and human variable regions including, among others, primers for $V_{H\alpha}$, $V_{H\beta}$, $V_{H\gamma}$, $V_{H\delta}$, C_{H1} , V_L and C_L regions, are available from Stratagene (La Jolla, Calif.). These primers may be utilized to amplify heavy or light chain variable regions, which may then be inserted into vectors such as 25 IMMUNOZAP™(H) or IMMUNOZAP™(L) (Stratagene), respectively. These vectors may then be introduced into *E. coli* for expression. Utilizing these techniques, large amounts of a single-chain polypeptide containing a fusion of the V_H and V_L domains may be produced (*see* Bird et al., *Science* 242:423-426, 1988).

Monoclonal antibodies and other binding partners can be produced in a number of host systems, including tissue cultures, bacteria, eukaryotic cells, plants and other host systems known in the art.

Once suitable antibodies or binding partners have been obtained, they 5 may be isolated or purified by many techniques well known to those of ordinary skill in the art (see *Antibodies: A Laboratory Manual*, Harlow and Lane (*supra*)). Suitable techniques include peptide or protein affinity columns, HPLC or RP-HPLC, purification on protein A or protein G columns, or any combination of these techniques. Within the context of the present invention, the term "isolated" as used to define antibodies or 10 binding partners means "substantially free of other blood components."

The binding partners of the present invention have many uses. For example, antibodies can be utilized in flow cytometry to identify cells bearing such a protein. Briefly, in order to detect the protein or peptide of interest on cells, the cells are incubated with a labeled monoclonal antibody which specifically binds to the 15 protein of interest, followed by detection of the presence of bound antibody. Labels suitable for use within the present invention are well known in the art including, among others, fluorescein isothiocyanate (FITC), phycoerythrin (PE), horse radish peroxidase (HRP), and colloidal gold. Particularly preferred for use in flow cytometry is FITC, which may be conjugated to purified antibody according to the method of Keltkamp in 20 "Conjugation of Fluorescein Isothiocyanate to Antibodies. I. Experiments on the Conditions of Conjugation," *Immunology* 18:865-873, 1970. (See also Keltkamp, "Conjugation of Fluorescein Isothiocyanate to Antibodies. II. A Reproducible Method," *Immunology* 18:875-881, 1970; Goding, "Conjugation of Antibodies with Fluorochromes: Modification to the Standard Methods," *J. Immunol. Methods* 13:215- 25 226, 1970.) The antibodies can also be used to target drugs to *Streptococcus* as well as a diagnostic for determining Streptococcal infection.

D. ASSAYS THAT UTILIZE THE HSP60 POLYPEPTIDES, OR ANTIBODIES THERETO, OF THE PRESENT INVENTION

A variety of assays can be utilized in order to detect the Hsp60 polypeptides from *Streptococcus pneumoniae* and *Streptococcus pyogenes* of the present invention, or antibodies that specifically bind to such Hsp60 polypeptides. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include: countercurrent immuno-electrophoresis (CIEP), 5 radioimmunoassays, radioimmunoprecipitations, enzyme-linked immuno-sorbent assays (ELISA), dot blot assays, inhibition or competition assays, and sandwich assays, immunostick (dipstick) assays, simultaneous immunoassays, immunochromatographic assays, immunofiltration assays, latex bead agglutination assays, immunofluorescent assays, biosensor assays, and low-light detection assays (see U.S. Patent Nos. 4,376,110 10 and 4,486,530; see also *Antibodies: A Laboratory Manual (supra)*).

A fluorescent antibody test (FA-test) uses a fluorescently labeled antibody able to bind to one of the proteins of the invention. For detection, visual determinations are made by a technician using fluorescence microscopy, yielding a qualitative result. In one embodiment, this assay is used for the examination of tissue 20 samples or histological sections.

In latex bead agglutination assays, antibodies to one or more of the proteins of the present invention are conjugated to latex beads. The antibodies conjugated to the latex beads are then contacted with a sample under conditions permitting the antibodies to bind to desired proteins in the sample, if any. The results 25 are then read visually, yielding a qualitative result. In one embodiment, this format can be used in the field for on-site testing.

Enzyme immunoassays (EIA) include a number of different assays able to utilize the antibodies provided by the present invention. For example, a heterogeneous indirect EIA uses a solid phase coupled with an antibody of the invention 30 and an affinity purified, anti-IgG immunoglobulin preparation. Preferably, the solid

phase is a polystyrene microtiter plate. The antibodies and immunoglobulin preparation are then contacted with the sample under conditions permitting antibody binding, which conditions are well known in the art. The results of such an assay can be read visually, but are preferably read using a spectrophotometer, such as an ELISA plate reader, to 5 yield a quantitative result. An alternative solid phase EIA format includes plastic-coated ferrous metal beads able to be moved during the procedures of the assay by means of a magnet. Yet another alternative is a low-light detection immunoassay format. In this highly sensitive format, the light emission produced by appropriately labeled bound antibodies are quantitated automatically. Preferably, the reaction is 10 performed using microtiter plates.

In an alternative embodiment, a radioactive tracer is substituted for the enzyme mediated detection in an EIA to produce a radioimmunoassay (RIA).

In a capture-antibody sandwich enzyme assay, the desired protein is bound between an antibody attached to a solid phase, preferably a polystyrene 15 microtiter plate, and a labeled antibody. Preferably, the results are measured using a spectrophotometer, such as an ELISA plate reader.

In a sequential assay format, reagents are allowed to incubate with the capture antibody in a step wise fashion. The test sample is first incubated with the capture antibody. Following a wash step, an incubation with the labeled antibody 20 occurs. In a simultaneous assay, the two incubation periods described in the sequential assay are combined. This eliminates one incubation period plus a wash step.

A dipstick/immunostick format is essentially an immunoassay except that the solid phase, instead of being a polystyrene microtiter plate, is a polystyrene paddle or dipstick. Reagents are the same and the format can either be simultaneous or 25 sequential.

In a chromatographic strip test format, a capture antibody and a labeled antibody are dried onto a chromatographic strip, which is typically nitrocellulose or nylon of high porosity bonded to cellulose acetate. The capture antibody is usually spray dried as a line at one end of the strip. At this end there is an absorbent material 30 that is in contact with the strip. At the other end of the strip the labeled antibody is

deposited in a manner that prevents it from being absorbed into the membrane. Usually, the label attached to the antibody is a latex bead or colloidal gold. The assay may be initiated by applying the sample immediately in front of the labeled antibody.

5 Immunofiltration/immunoconcentration formats combine a large solid phase surface with directional flow of sample/reagents, which concentrates and accelerates the binding of antigen to antibody. In a preferred format, the test sample is preincubated with a labeled antibody then applied to a solid phase such as fiber filters or nitrocellulose membranes or the like. The solid phase can also be precoated with latex or glass beads coated with capture antibody. Detection of analyte is the same as 10 standard immunoassay. The flow of sample/reagents can be modulated by either vacuum or the wicking action of an underlying absorbent material.

A threshold biosensor assay is a sensitive, instrumented assay amenable to screening large numbers of samples at low cost. In one embodiment, such an assay comprises the use of light addressable potentiometric sensors wherein the reaction 15 involves the detection of a pH change due to binding of the desired protein by capture antibodies, bridging antibodies and urease-conjugated antibodies. Upon binding, a pH change is effected that is measurable by translation into electrical potential (μ volts). The assay typically occurs in a very small reaction volume, and is very sensitive. Moreover, the reported detection limit of the assay is 1,000 molecules of urease per 20 minute.

The present invention also provides for probes and primers for detecting *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

In one embodiment of this aspect of the invention, probes are provided that are capable of specifically hybridizing to *S. pneumoniae* and *S. pyogenes* Hsp60 25 genes DNA or RNA. For purposes of the present invention, probes are "capable of hybridizing" to *S. pneumoniae* and *S. pyogenes* Hsp60 genes DNA or RNA if they hybridize under conditions of high stringency (see Sambrook et al. (*supra*)). Preferably, the probe may be utilized to hybridize to suitable nucleotide sequences under highly stringent conditions, such as 6x SSC, 1x Denhardt's solution (Sambrook et al. (*supra*)), 30 0.1% SDS at 65°C and at least one wash to remove excess probe in the presence of 0.2x

SSC, 1x Denhardt's solution, 0.1% SDS at 65°C. Except as otherwise provided herein, probe sequences are designed to allow hybridization to Streptococcal DNA or RNA sequences, but not to DNA or RNA sequences from other organisms, particularly other bacterial sequences. The probes are used, for example, to hybridize to nucleic acid that 5 has been exposed from a cell in a sample. The hybridized probe is then detected, thereby indicating the presence of the desired cellular nucleic acid. Preferably, the cellular nucleic acid is subjected to an amplification procedure, such as PCR, prior to hybridization.

Probes of the present invention may be composed of either 10 deoxyribonucleic acids (DNA) or ribonucleic acids (RNA), and may be as few as about 12 nucleotides in length, usually about 14 to 18 nucleotides in length, and possibly as large as the entire sequence of the *S. pneumoniae* and *S. pyogenes* Hsp60 genes. Selection of probe size is somewhat dependent upon the use of the probe, and is within the skill of the art.

15 Suitable probes can be constructed and labeled using techniques that are well known in the art. Shorter probes of, for example, 12 bases can be generated synthetically. Longer probes of about 75 bases to less than 1.5 kb are preferably generated by, for example, PCR amplification in the presence of labeled precursors such as [α -32P]dCTP, digoxigenin-dUTP, or biotin-dATP. Probes of more than 1.5 kb are 20 generally most easily amplified by transfecting a cell with a plasmid containing the relevant probe, growing the transfected cell into large quantities, and purifying the relevant sequence from the transfected cells. (See Sambrook et al. (*supra*)).

Probes can be labeled by a variety of markers, including for example, radioactive markers, fluorescent markers, enzymatic markers, and chromogenic 25 markers. The use of 32P is particularly preferred for marking or labeling a particular probe.

It is a feature of this aspect of the invention that the probes can be utilized to detect the presence of *S. pneumoniae* and *S. pyogenes* Hsp60 mRNA or DNA within a sample. However, if the bacteria are present in only a limited number, then it

may be beneficial to amplify the relevant sequence such that it may be more readily detected or obtained.

A variety of methods may be utilized in order to amplify a selected sequence, including, for example, RNA amplification (see Lizardi et al., 5 *Bio/Technology* 6:1197-1202, 1988; Kramer et al., *Nature* 339:401-402, 1989; Lomeli et al., *Clinical Chem.* 35(9):1826-1831, 1989; U.S. Patent No. 4,786,600), and DNA amplification utilizing LCR or Polymerase Chain Reaction ("PCR") (see U.S. Patent Nos. 4,683,195, 4,683,202, and 4,800,159; *see also* U.S. Patent Nos. 4,876,187 and 5,011,769, which describe an alternative detection/amplification system comprising the 10 use of scissile linkages), or other nucleic acid amplification procedures that are well within the level of ordinary skill in the art. With respect to PCR, for example, the method may be modified as known in the art. PCR may also be used in combination with reverse dot blot hybridization (Iida et al., *FEMS Microbiol. Lett.* 114:167-172, 1993). PCR products may be quantitatively analyzed by incorporation of dUTP 15 (Dupl  a et al., *Anal. Biochem.* 212:229-236, 1993), and samples may be filter sampled for PCR-gene probe detection (Bej et al., *Appl. Environ. Microbiol.* 57:3529-3534, 1991).

Within a preferred embodiment, PCR amplification is utilized to detect *S. pneumoniae* and *S. pyogenes* Hsp60 DNA. Briefly a DNA sample is denatured at 95° 20 C in order to generate single-stranded DNA. Specific primers are then annealed to the single-stranded DNA at 37°C to 70°C, depending on the proportion of AT/GC in the primers. The primers are extended at 72°C with *Taq* DNA polymerase in order to generate the opposite strand to the template. These steps constitute one cycle, which may be repeated in order to amplify the selected sequence.

25 Within an alternative preferred embodiment, LCR amplification is utilized for amplification. LCR primers are synthesized such that the 5' base of the upstream primer is capable of hybridizing to a unique base pair in a desired gene to specifically detect a strain of *Streptococcus* harboring the desired gene.

Within another preferred embodiment, the probes are used in an 30 automated, non-isotopic strategy wherein target nucleic acid sequences are amplified by

PCR, and then desired products are determined by a colorimetric oligonucleotide ligation assay (OLA) (Nickerson et al., *Proc. Natl. Acad. Sci. USA* 81:8923-8927, 1990).

Primers for the amplification of a selected sequence should be selected 5 from sequences that are highly specific and form stable duplexes with the target sequence. The primers should also be non-complementary, especially at the 3' end, should not form dimers with themselves or other primers, and should not form secondary structures or duplexes with other regions of DNA. In general, primers of about 18 to 20 nucleotides are preferred, and can be easily synthesized using techniques 10 well known in the art. PCR products, and other nucleic acid amplification products, may be quantitated using techniques known in the art (Dupl  a et al., *Anal. Biochem.* 212:229-236, 1993; Higuchi et al., *Bio/Technology* 11:1026-1030).

Further a biochip array specific for *Streptococcus*, comprised of a substrate to which either oligonucleotides or polypeptides may be bound can be 15 manufactured using the invention disclosed herein in combination with current biochip technologies. U.S. Patent No. 5,445,934. By using such a substrate with oligonucleotides derived from the Streptococcal Hsp60 sequences or antibodies specific for the Streptococcal gene products of this invention, a high throughput screening tool can be created to identify the specific Streptococcal strain in many samples.

20

E. PHARMACEUTICAL COMPOSITIONS AND METHODS

Another aspect of the present invention provides compositions and methods comprising one or more of the above-described Streptococcal Hsp60 polypeptides or antibodies to Streptococcal Hsp60 in combination with one or more 25 pharmaceutically or physiologically acceptable carriers, adjuvants, binders or diluents. Such compositions can be used to elicit or enhance an immune response in a recipient animal, which is preferably a human being, and preferably elicits or enhances a protective or partially protective immunity against *Streptococcus*, or against an organism associated with an antigen fused to the Streptococcal Hsp60s of the present 30 invention.

Preferably, such carriers, adjuvants, binders or diluents are nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the isolated Streptococcal Hsp60 polypeptide with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents. Examples of adjuvants include alum or aluminum hydroxide for humans.

It will be evident in light of the present specification to those in the art that the amount and frequency of administration can be optimized in clinical trials, and will depend upon such factors as the disease or disorder to be treated, the degree of immune inducement, enhancement, or protection required, and many other factors.

In one embodiment, the composition is administered orally, and the purified Streptococcal Hsp60 is taken up by cells, such as cells located in the lumen of the gut. Alternatively, the Streptococcal Hsp60 composition can be parenterally administrated via the subcutaneous route, or via other parenteral routes. Other routes include buccal/sublingual, rectal, nasal, topical (such as transdermal and ophthalmic), vaginal, pulmonary, intraarterial, intramuscular, intraperitoneal, intraocular, intranasal or intravenous, or indirectly. The Streptococcal Hsp60 compositions of the present invention can be prepared and administered as a liquid solution, or prepared as a solid form (e.g., lyophilized) which can be administered in solid form or resuspended in a solution in conjunction with administration.

Depending upon the application, quantities of injected Streptococcal Hsp60 in the composition will vary generally from about 0.1 μ g to 1000 mg, typically from about 1 μ g to 100 mg, preferably from about 10 μ g to 10 mg, and preferably from about 100 μ g to 1 mg, in combination with the physiologically acceptable carrier, binder or diluent. Booster immunizations can be given from 2-6 weeks later.

The pharmaceutical compositions of the present invention may be placed within containers, along with packaging material, preferably consumer-acceptable,

which provides instructions regarding the use of such pharmaceutical compositions, to provide kits suitable for use within the present invention. Generally, such instructions will include a tangible expression describing the reagent concentration, as well as within certain embodiments, relative amounts of excipient ingredients or diluents (e.g., 5 water, saline or PBS) which may be necessary to reconstitute the pharmaceutical composition.

The Hsp gene products of this invention may also be used as immunological carriers in conjugate vaccines. Hsps are beneficial carriers of antigens because, unlike other carriers, they do not have an immunosuppressive effect. See 10 Barrios et al., *Eur. J. Immunol.* 22:1365-1372, 1992; Suzue and Young, in *Stress-Inducible Cellular Responses* 77:451-465, 1996 (edited by U. Feige et al.). Such carriers may be used to elicit an increased immune response to the conjugated molecule. The Streptococcal Hsp gene products of this invention may therefore be used as carriers (in conjugates or fusion proteins).

15 An additional aspect of the present invention is the use of the Streptococcal Hsp60 genes and gene products to treat and/or prevent tumors. The methods comprise administering to an individual having cancer a composition comprising a purified Streptococcal Hsp60 gene product as discussed herein in an amount effective to elicit and/or enhance the immune response of an individual against 20 the cancer. The present invention also provides a method of immunizing an individual against cancer, or of providing at least a partially effective immunoprotective response in such an individual, the method comprising administering to the individual a composition comprising a purified Streptococcal Hsp60 as discussed herein in an amount effective to immunize the individual.

25 Preferably, the treatment of cancer comprises the use of highly purified Streptococcal Hsp60 gene products that are substantially free of endotoxins and methods and compositions related to the same. Such highly purified proteins are particularly advantageous, for example, for the treatment of human cancers because they do not incur the adverse side effects associated with such endotoxins. In particular, 30 the compositions are capable of inducing an immune response against a cancer existing

within an individual, which includes both eliciting the immune response or enhancing the immune response against the cancer. For example, the cancer to be treated may be an endothelial cell cancer, such as a sarcoma and/or breast, ovarian, prostate, lung, pancreas and liver cancers. The present invention also provides compositions that are 5 capable of providing either partially or fully protective immune responses by immunization against cancers that are not yet present within an individual.

A further aspect of the present invention is protection from a variety of bacterial diseases by either immunization with the Hsp60 gene products of the present invention or by using gene transfer techniques to deliver a vector containing 10 Streptococcal Hsp60 genes or fragments thereof to be expressed within the cells of the animal. The compositions and methods of the present invention can also provide for cancer prevention.

The compositions and methodologies described herein are suitable for a variety of uses. To this end, the following examples are presented for purposes of 15 illustration, not limitation.

EXAMPLES

EXAMPLE 1

20 ISOLATION OF GENES FOR STREPTOCOCCUS PNEUMONIAE AND STREPTOCOCCUS PYOGENES HSPS

Genomic DNA from *Streptococcus pneumoniae* (ATCC6314) and *Streptococcus pyogenes* (ATCC12344), prepared by a routine method, was obtained 25 from Dr. Lee Weber, University of Nevada at Reno.

Hsp60 DNA sequences were isolated by use of the polymerase chain reaction. Primers were designed based on N- and C-terminal homology of known Hsp60 sequences from other organisms. DNA amplifications of Streptococcal DNA were carried out using Taq polymerase (Perkin-Elmer). About 20 different primer pairs 30 were tested using different reaction conditions. One pair (pair 1) was identified that was

capable of amplifying Hsp60-1 genes, and a second (pair 2) that permitted amplification of Hsp60-2 sequences. Reaction mixtures capable of amplifying Hsp60 sequences contained, in a total volume of 50 μ l, 0.5 μ g of genomic DNA, 50 pmoles of each of a pair of degenerate primers, 500 μ M each of dNTPs, 1xPCR buffer (Perkin-Elmer), 2 5 mM MgSO₄, and 1.25 units of Taq polymerase (Perkin-Elmer). The following two pairs of degenerate primers were employed successfully:

Pair 1:

forward primer #1F: 5'-CATATGGCNGCNAAGAYGTAAAA-3' (SEQ ID NO:35)

10 reverse primer #1R: 5'-TGATCACATCATNCCNCCATNCC-3' (SEQ ID NO:36)

Pair 2:

forward primer #2F: 5'-CATATGGCAAAAGAAATHAARTTY-3' (SEQ ID NO:37)

reverse primer #2R: 5'-TGATCANCCNCCATNCCNCCAT-3' (SEQ ID NO:38)

15

In the above sequences, N refers to A, C, G or T, and H to A, C or T (not G).

Reactions were cycled 35 times at 94°C for 1 minute, 50°C for 2 minutes and 72°C for 2 minutes. PCR products were electrophoresed on 0.6% low-melting point 20 agarose gels (Gibco-BRL) along with molecular weight markers. After staining with ethidium bromide, DNA fragments were visualized under low-intensity, long-wavelength UV illumination, and fragments of about 1.6 kbp were excised. DNA was isolated from gel slices by phenol extraction and ethanol precipitation (Maniatis et al.). Purified fragments were ligated to pCRII TA cloning vector (Invitrogen), and ligation 25 mixtures were used to transform *E. coli* strain DH5a. (Competent cells obtained from Life Technologies.) Recombinant plasmids were isolated from kanamycin-resistant colonies by a standard alkaline lysis method, and the presence in plasmids of DNA inserts was verified by digestion with EcoRI digestion followed by agarose gel electrophoresis and visualization of digestion products by staining with ethidium 30 bromide.

EXAMPLE 2

NUCLEOTIDE SEQUENCE ANALYSIS OF STREPTOCOCCAL HSP60

5 Inserts present in recombinant pCRII-based clones were sequenced using a CircumVent sequencing kit (New England Biolabs), ^{35}S -dATP and primers listed below. Multiple clones containing particular Streptococcal *Hsp60* genes were sequenced: sequences were obtained from five clones, derived from three independent PCR reactions, of the *Streptococcus pneumoniae* *Hsp60-1* gene, two clones, derived 10 from single PCR reactions, of the *Streptococcus pneumoniae* *Hsp60-2* gene, four clones, derived from three independent PCR reactions, of the *Streptococcus pyogenes* *Hsp60-1* gene, and two clones and a portion of a third clone, derived from single PCR reaction, of the *Streptococcus pyogenes* *Hsp60-2* gene. Sequencing reactions were fractionated on denaturing 6% polyacrylamide-8M urea gels (60 cm length), and the 15 gels were dried and exposed for autoradiography. Autoradiographs were read manually, and sequence data were assembled and compared to other known *Hsp60* genes using DNA Strider software (CEA, France).

Sequencing primers used:

20 M13F : 5'-GTAAAACGACGGCCAG-3' (SEQ ID NO:39)
 M13R : 5'-CAGGAAACAGCTATGAC-3' (SEQ ID NO:40)
 W178 : 5'-CCAACCATCACGAAAGA-3' (SEQ ID NO:41)
 W179 : 5'-ACGGGTCACTTGGTTG-3' (SEQ ID NO:42)
 25 W189 : 5'-TTACTAATGACGGGTA-3' (SEQ ID NO:43)
 W190 : 5'-TTACCAATGACGGTGTG-3' (SEQ ID NO:44)
 W191 : 5'-ACAGGGTCAATGATTCC-3' (SEQ ID NO:45)
 W192 : 5'-ACTGGATCAATGATACC-3' (SEQ ID NO:46)
 W195 : 5'-CCGTACCGTGCTCTGAC-3' (SEQ ID NO:47)
 30 W196 : 5'-ACCACGTTCAGATCCA-3' (SEQ ID NO:48)

W197 : 5'-GACAGTTCGCGGCAAC-3' (SEQ ID NO:49)
W198 : 5'-CTCAGAACGAAGATCAG-3' (SEQ ID NO:50)
W200 : 5'-GGTATGCAGTCGACCG-3' (SEQ ID NO:51)
W201 : 5'-CCGTGTTGGTCAAATCC-3' (SEQ ID NO:52)
5 W202 : 5'-GGTAAC TACGGTTACAA-3' (SEQ ID NO:53)
W203 : 5'-GAGGCCACTTCTTCAC-3' (SEQ ID NO:54)
W204 : 5'-GGCTTCCAGCACTGGCA-3' (SEQ ID NO:55)
W205 : 5'-AACTTCAGTCGCAGCAC-3' (SEQ ID NO:56)
W206 : 5'-CCTGAAAGCCATTGCT-3' (SEQ ID NO:57)
10 W207 : 5'-GCTACACGTGCAGCCGT-3' (SEQ ID NO:58)
W208 : 5'-GCTGCAACAGGTGAGTG-3' (SEQ ID NO:59)
W209 : 5'-TCATGAACAATGGCTTG-3' (SEQ ID NO:60)
W210 : 5'-ACGAAGCACAATGTTAC-3' (SEQ ID NO:61)
W211 : 5'-ATCACTAAAGATGGTGT-3' (SEQ ID NO:62)
15 W214 : 5'-GCAGTTGCCGCAGCAGT-3' (SEQ ID NO:63)
W215 : 5'-GCTACTCGTGCAGCTGT-3' (SEQ ID NO:64)
W216 : 5'-GTTCTCCGTGCTTGGGA-3' (SEQ ID NO:65)
W217 : 5'-GCACCTGCTGTGACGTT-3' (SEQ ID NO:66)
W218 : 5'-TCTTCGATGGTGATGAC-3' (SEQ ID NO:67)
20 W219 : 5'-GGCAAGAGCTGTTCCGC-3' (SEQ ID NO:68)
W220 : 5'-CTGAGCCAGTACGGTTG-3' (SEQ ID NO:69)
W221 : 5'-GTACTGCAGAGCGGAAC-3' (SEQ ID NO:70)
W224 : 5'-ACCGTCTTCAACGGTGA-3' (SEQ ID NO:71)
W225 : 5'-GTTATCATTGCTGAAGA-3' (SEQ ID NO:72)
25 W226 : 5'-ACGGTACCGCCGGTCAG-3' (SEQ ID NO:73)
W227 : 5'-CTGGGCCAGGCTAAACG-3' (SEQ ID NO:74)
W228 : 5'-CGACTGAAGTTGAAATG-3' (SEQ ID NO:75)
W229 : 5'-GCTGTTGAAGAACTGAA-3' (SEQ ID NO:76)
W230 : 5'-GTCTTCAACGGTGATCA-3' (SEQ ID NO:77)
30 W232 : 5'-TCTTCTACCGCAGCACG-3' (SEQ ID NO:78)

W233 : 5'-CTCTGATTATTGCGGA-3' (SEQ ID NO:79)
W234 : 5'-TTGTTCAAAACAAGAGT-3' (SEQ ID NO:80)
W235 : 5'-CGATTATTGTAGAAGGT-3' (SEQ ID NO:81)
W236 : 5'-CTTGATAACCGCAACAC-3' (SEQ ID NO:82)
5 W237 : 5'-TCCAAAGCACGGAGAAC-3' (SEQ ID NO:83)
W238 : 5'-GTGTCAAACATCCAAGA-3' (SEQ ID NO:84)
W239 : 5'-TCTTCGATGGTAATCAC-3' (SEQ ID NO:85)
W240 : 5'-GCAATAATGAGTAATGG-3' (SEQ ID NO:86)
W241 : 5'-ACAGTAATTGTTGAAGG-3' (SEQ ID NO:87)
10 W242 : 5'-CAGTGCAATACGGTTAG-3' (SEQ ID NO:88)
W243 : 5'-AGCTTCCAGAACCGGCA-3' (SEQ ID NO:89)
W244 : 5'-CTGATCATCGCTGAAGA-3' (SEQ ID NO:90)
W245 : 5'-ACGGTTATTGTAGAAG-3' (SEQ ID NO:91)

15 The sequencing strategy for each of the Hsp60 genes is set forth in Figure 5. The nucleotide sequences of the *Streptococcus pneumoniae* Hsp60-1 gene (referred to as P60-1), the *Streptococcus pneumoniae* Hsp60-2 gene (P60-2), the *Streptococcus pyogenes* Hsp60-1 gene (Y60-1) and the *Streptococcus pyogenes* Hsp60-2 gene (Y60-2), and the corresponding deduced amino acid sequences, are set forth in
20 Figures 1-4 (SEQ ID NOS:1-8).

Comparisons of Streptococcal Hsp60 proteins and mycobacterial Hsp65 and GroEL proteins were determined using the MegAlign module of a DNA Star software package (DNASTAR, Inc.), and sequence similarities to Genbank-listed genes and proteins were uncovered using the BLAST algorithm (National Center for
25 Biotechnology Information, NIH, Bethesda, MD). One comparison of such sequences is set forth in Figure 10.

EXAMPLE 3

EXPRESSION OF RECOMBINANT STREPTOCOCCAL HSP60

5 Inserts (*Hsp60 genes*) were excised from recombinant pCRII-based plasmids with restriction enzymes NdeI and EcoRI. NdeI cut inside forward PCR primers #1F or #2F, and EcoRI cut a short distance downstream from reverse PCR primers #1R or #2R in the polylinker region of vector PCRII. DNA fragments including *Hsp60* gene sequences were fractionated on low-melting-point agarose gels, purified from the gels and ligated into NdeI/EcoRI double-digested pET28a(+) vector

10 10 DNA (Novagen). Ligation reactions were used to transform competent *Escherichia coli* DH5a cells, and transformants were selected on Luria Broth plates containing 30µg/ml of kanamycin D. DNA was isolated from single colonies using a standard alkaline lysis method, and the presence of correct inserts verified by digestion with NdeI and EcoRI and agarose gel electrophoresis. The resulting expression plasmids contained either a

15 15 *Streptococcus pneumoniae Hsp60-1* gene (referred to as pETP60-1), a *Streptococcus pneumoniae Hsp60-2* gene (pETP60-2), a *Streptococcus pyogenes Hsp60-1* gene (pETY60-1) or a *Streptococcus pyogenes Hsp60-2* gene (pETY60-2). Schematic maps of the expression plasmids are shown in Figures 6-9.

To test whether they were capable of expressing the inserted 20 Streptococcal *Hsp60* genes, the expression plasmids were introduced into *Escherichia coli* strain BL21(DE3) by electroporation, and transformant colonies were selected on kanamycin-containing plates as before. Cultures of one ml were inoculated with single colonies, and transformants were grown at 37°C, until the cultures were turbid. After removing an aliquot for analysis of proteins prior to induction of recombinant genes 25 (uninduced cultures), isopropyl-thio-galactopyranoside (IPTG) was added to 1mM, and cultures were incubated for an additional one or two hours (induced cultures). Aliquots of 100µl of induced and uninduced cultures were centrifuged at 12,000 x g for 30 seconds. Bacterial pellets were lysed in 100µl of SDS-PAGE loading buffer and boiled for 3 minutes. Aliquots of 10µl of lysates were analyzed by 10% SDS-PAGE. 30 Recombinant Streptococcal Hsp60 proteins were detectable after Coomasie blue

staining as prominent bands migrating with an apparent molecular weight of about 60kDa, which bands were present in induced but not in uninduced samples.

EXAMPLE 4

5 PURIFICATION OF RECOMBINANT STREPTOCOCCAL HSP60

Bacteria containing recombinant Streptococcal *Hsp60* expression plasmids were grown in 2xYT medium (20 g Tryptone, 10 g yeast extract, 10 g NaCl per liter) supplemented with 30 μ g/ml of kanamycin D at 37°C to an optical density at 10 600 nm of 0.5-0.8 and then induced with 0.5 mM IPTG for 3 hours. Cultures were then chilled on ice, and bacteria collected by centrifugation at 7,000 x g for 5 min (at 4°C). Bacterial pellets were frozen at -80°C.

15 Frozen bacterial pellet was crushed, transferred to a blender and homogenized in 200ml of buffer A (6 M guanidinium hydrochloride, 50 mM Tris-HCl pH 7.5, 0.5 mM beta-mercaptoethanol).

20 Lysate was cleared by centrifugation at 10,000 x g for 15 min (at 4°C). The supernatant solution was mixed overnight at room temperature with approximately 100ml of slurry containing 50ml of Ni-Sepharose (Chelating Sepharose, Pharmacia) equilibrated in buffer A. The resin was then washed on filter paper with approximately 200 ml buffer A, resuspended in small volume of the same buffer and gravity-packed into glass chromatography column (Pharmacia).

25 The column was washed with 20 ml of buffer A with 1% Triton X-100. The column was further washed with a 6 - 0 M guanidinium hydrochloride / 0 - 1 M NaCl gradient in 50 mM Tris-HCl pH 7.5, 0.5 mM beta-mercaptoethanol (200ml), then with 200 ml of 50 mM Tris-HCl pH 7.5, 1 M NaCl, 0.5 mM beta-mercaptoethanol, and finally with 200 ml of 50 mM imidazole, 0.5 M NaCl, 50 mM Tris-HCl pH 7.5, 1.025 M NaCl, 0.5 mM beta-mercaptoethanol. Then column was developed with a 200ml-gradient from 5% to 100% of buffer composed of 1 M imidazole, 0.5 M NaCl, 50 mM Tris-HCl pH 7.5, 0.5 mM beta-mercaptoethanol in 1M NaCl, 50 mM Tris-HCl pH 7.5,

0.5 mM beta-mercaptoethanol. Fractions of 9ml were collected. The flow rate was 4-5 ml/min, and chromatography was monitored by absorbance at 280 nm.

5 Fractions containing the highest concentrations of recombinant protein were identified by 10% SDS-PAGE as before, pooled (usually 5-6 fractions) into a dialysis bag (12 kDa cutoff). Protein solution (approximately 50 ml) was then dialysed in the cold against three changes of 3 liters of Dulbeccos' phosphate-buffered saline (2.7 mM KH₂PO₄, 4.3 mM Na₂HPO₄, 2.7 mM KCl, 0.137 M NaCl). Dialysed protein was aliquoted and stored at -80°C. Usually 200-400 mg of recombinant protein were obtained (estimated by protein assay according to Lowry).

10

EXAMPLE 5

CHARACTERIZATION OF PURIFIED, RECOMBINANT HSP60

15 To unambiguously identify recombinant proteins as Streptococcal Hsp60, purified recombinant proteins were subjected to N- and C-terminal sequencing (conducted by the Protein Chemistry Facility, W. Alton Jones Cell Science Center, Lake Placid, NY). These determinations revealed that purified recombinant proteins had the C- and N-terminal sequences predicted from the deducted amino acid sequences of SEQ ID NOS:5-8 (except for the 20 N-terminal methionine that is typically processed away in *E. coli* bacteria).

EXAMPLE 6

REACTIVITY OF RECOMBINANT STREPTOCOCCAL HSP60 WITH KNOWN ANTI-HSP60 MONOCLONAL ANTIBODIES

25

Purified recombinant Streptococcal Hsp60 proteins were analyzed for reactivity with the following commercially available antibodies:

30 A) Rabbit polyclonal antibody SPA-804 (StressGen Biotechnologies) which was raised against *Synechococcus sp.* Hsp60. The antibody recognizes Hsp60 from a wide range of prokaryotes and eukaryotes

including cyanobacteria, *Escherichia coli*, and primate, murine, hamster, and rat cell lines.

5 B) Murine monoclonal antibody SPA-807 (StressGen Biotechnologies) which was raised against human Hsp60. Its epitope is located between residues 383-419 of that protein. The antibody also cross-reacts with Hsp60 from various other species including primates, rabbit, mouse, rat, hamster, *Borrelia* sp., *Escherichia coli*, *Streptococcus pyogenes*, *Yersinia enterocolitica*, *Salmonella typhimurium*, *Treponema hyodysenteriae*, *Treponema innocense*, 10 *Trichinella spiralis*, yeast, and spinach chloroplasts.

15 C) Murine monoclonal antibody SPA-870 (StressGen Biotechnologies) which was raised against *Escherichia coli* GroEL. The antibody does not recognize eukaryotic Hsp60 proteins.

D) Murine polyclonal antibody which was raised against *Mycobacterium tuberculosis* BCG Hsp60 (StressGen Biotechnologies). The antibody does not cross-react with *Escherichia coli* groEL or eukaryotic Hsp60.

20 E) Murine monoclonal antibody recognizing recombinant histidine tag (Qiagen).

20 Samples containing 0.1 μ g, 0.5 μ g or 1 μ g of recombinant protein were fractionated on 10% SDS-PAGE, and proteins were electroblotted onto nitrocellulose. Blots for analysis with antibodies SPA-804, SPA-807, SPA-870, and anti-BCG Hsp60 were blocked with 5% skim milk in PBS containing 0.05% Tween 20 overnight at room 25 temperature. Blots were then incubated for one hour in the same buffer containing primary antibody (at a 1:1000 dilution except for anti-BCG Hsp60 antibody which was used at a 1:500 dilution). Blots were washed 3 times (10 min each) with PBS with 0.05% Tween 20 and incubated for an additional hour in PBS with 5% skim milk, 0.05% Tween 20 and goat anti-rabbit IgG - alkaline phosphatase (AP) conjugate 30 (Sigma) or goat-anti-murine IgG - alkaline phosphatase (AP) conjugate (Sigma) (at

1:1000 dilutions), respectively. After 3 washes in PBS with 0.05% Tween 20 as before, blots were soaked in alkaline phosphatase reaction buffer (100 mM Tris-HCl (pH 9.5), 150 mM NaCl, 10 mM MgCl₂) and then developed in 0.05% nitroblue tetrazolium (NBT), 0.05% 5-bromo-4-chloro-3-indolyl phosphate (BCIP) in the same buffer, until 5 signals were clearly visible (approximately 15 minutes).

A similar procedure was followed for anti-histidine tag antibody, except that blocking was in 3% bovine serum albumin in TBS (10 mM Tris-HCl, pH 7.5, 150 mM NaCl). Primary and secondary antibodies were diluted in TBS alone, and incubation with primary antibody (1:500 dilution) was for two hours. Washes were 10 performed as follows: blots were first washed twice for 10 min in TBS containing 0.05% Tween 20 and 0.2% Triton X-100, and once for 10 min in TBS.

Recombinant histidine-tagged Hsp60 proteins were purified from overexpressing *E. coli* cells and probed on Western blot with polyclonal antibodies SPA-804 and anti-BCG Hsp60 as well as monoclonal antibodies SPA-870, SPA-807, 15 and anti-histidine tag antibody. As is shown in Table 1, SPA-804 recognized all four Streptococcal Hsp60 proteins. In contrast, SPA-807 failed to crossreact with *Streptococcus pneumoniae* Hsp60-2, SPA-870 was unable to react with any Streptococcal Hsp60-2 protein, and anti-BCG Hsp60 failed to crossreact with any 20 Streptococcal Hsp60. As predicted, anti-His tag antibody reacted with all recombinant proteins which had been expressed as His-tagged proteins. Positive reactivity is indicated as "+" while lack of it is marked with "-".

TABLE 1

25 RECOGNITION OF STREPTOCOCCAL HSP60 PROTEINS BY ANTI-HSP60 ANTIBODIES

Antibody	<i>S. pneumoniae</i> Hsp60-1	<i>S. pneumoniae</i> Hsp60-2	<i>S. pyogenes</i> Hsp60-1	<i>S. pyogenes</i> Hsp60-2
SPA-804	+	+	+	+
SPA-807	+	-	+	+
SPA-870	+	-	+	-
anti-BCG60	-	-	-	-
anti-His tag	+	+	+	+

These data demonstrate that Streptococcal Hsp60 are antigenically distinct from Hsp60 of other organisms. They also show that Streptococcal Hsp60-1 and Hsp60-2 can be distinguished. And, they provide evidence that related Hsp60s 5 from two different Streptococcal species can be recognized differentially by an antibody.

EXAMPLE 7

PREPARATION AND IDENTIFICATION OF PEPTIDE FRAGMENTS OF RECOMBINANT STREPTOCOCCAL HSP60

10

Purified recombinant proteins (50 mg at 1 mg/ml) were digested with 2.5 mg of Lys-C endopeptidase (Boehringer Mannheim) for 1 hour at 37°C. Digestion reactions were fractionated by capillary electrophoresis (3D-HPCE instrument, Hewlett-Packard). Reactions were run at 15 kV through a 75 u bare fused silica capillary in 50 15 mM dibasic sodium phosphate (pH 7.47). Alternatively, reverse phase chromatography (1100 Series HPLC instrument, Hewlett-Packard) was carried out on a Hamilton PRP-1 5 m column developed in a 0-60% acetonitrile gradient in water in the presence of 0.1% trifluoroacetic acid. Individual RP-HPLC-separated peptides of Hsp60 proteins were identified by mass spectroscopy by Hewlett-Packard Laboratories, Palo Alto, 20 California. RP-HPLC chromatograms of digests of recombinant Streptococcal Hsp60s are shown in Figure 11.

EXAMPLE 8

IDENTIFICATION OF ENDOGENOUS STREPTOCOCCAL HSP60

25

Total protein extracts from *Streptococcus pneumoniae* (ATCC6314) and *Streptococcus pyogenes* (ATCC12344) were obtained from Dr. Lee Weber (University of Nevada, Reno). Equivalent amounts of both extracts (equalized based on intensity of staining of protein bands in SDS-PAGE gels) were fractionated by 10% SDS-PAGE 30 alongside 50 ng of purified BGC Hsp60 (StressGen Biotechnologies). After

electrotransfer onto nitrocellulose, filters were blocked, probed with antibody SPA-804, and antibody signals detected as described in Example 6.

Other, similarly prepared filters were incubated with a 1:3000 dilutions of antibodies SPA-807 or SPA-870 for one hour. Blots were rinsed twice with water, 5 washed 3 times (5 min each) with PBS containing 0.05% Tween 20 and then incubated for an additional hour in PBS containing 5% skim milk, 0.05% Tween 20 and a 1:3000 dilution of goat anti-rabbit IgG - horseradish peroxidase (HRP) conjugate (Sigma). Subsequently, filters were rinsed with water, washed with PBS containing 0.05% Tween 20 as before, equilibrated in ECL substrate mixture (Amersham), wrapped in 10 plastic wrap and exposed to X-ray film for between 15 seconds and 20 minutes.

The results from these experiments are summarized in Table 2. Antibody SPA-804 reacted strongly with both Streptococcal extracts. In contrast, antibody SPA-807 reacted weakly with extract from *Streptococcus pneumoniae* but strongly with extract from *Streptococcus pyogenes*. Finally, antibody SPA-870 reacted 15 weakly with both Streptococcal extracts. Based on the antibody specificity determined in Example 6 (Table 1), it is concluded that Hsp60-2 is abundant in Streptococcal cells, whereas Hsp60-1 is only expressed at low levels. Presumably, Hsp60-1 is the more highly stress-inducible Hsp60 protein.

20

TABLE 2

REACTIVITY OF SELECTED ANTI-HSP60 ANTIBODIES WITH PROTEIN EXTRACTS FROM
S. PNEUMONIAE AND *S. PYOGENES*

Antibody	BCG60 control (50 ng)	<i>S. pneumoniae</i> extract	<i>S. pyogenes</i> extract
SPA-804	+++	+++	+++
SPA-807	+++	+	+++
SPA-870	-	+	+ a

25

a: SPA870 detected protein with mobility different from predominant heavy band visualized in that extract with SPA-807. However, its mobility was close to the band detected in *S. pneumoniae* extract with both SPA-870 and SPA-807 antibodies.

The amount of the utilized extracts was normalized by comparing Coomassie stained gels containing serial dilutions.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. An isolated nucleic acid molecule encoding a *Streptococcus pneumoniae* Hsp60.
2. An isolated nucleic acid molecule encoding a *Streptococcus pyogenes* Hsp60.
3. An isolated nucleotide molecule selected from the group consisting of:
 - (a) an isolated nucleic acid molecule comprising the sequence of SEQ ID NO:1 from nucleotides 15-1652;
 - (b) an isolated nucleic acid molecule comprising the sequence of SEQ ID NO:3 from nucleotides 15-1640;
 - (c) an isolated nucleic acid molecule comprising the sequence of SEQ ID NO:5 from nucleotides 15-1649;
 - (d) an isolated nucleic acid molecule comprising the sequence of SEQ ID NO:7 from nucleotides 15-1652;
 - (e) an isolated nucleic acid molecule complementary to any one of the nucleotides of SEQ ID NOS:1, 3, 5 or 7 set forth in (a) through (d), respectively; and
 - (f) an isolated nucleic acid molecule that hybridizes under conditions of high stringency to the nucleic acid molecules of any one of (a) through (e).
4. An isolated nucleic acid molecule that specifically hybridizes to the nucleic acid molecule of any one of SEQ ID NO:1 from nucleotides 15-1652, SEQ ID NO:3 from nucleotides 15-1640, SEQ ID NO:5 from nucleotides 15-1649, or SEQ ID NO:7 from nucleotides 15-1652 or a complement thereof under conditions of high stringency.
5. An isolated nucleic acid molecule comprising a nucleotide sequence that is identical to a segment comprising at least 25% of contiguous nucleotide bases of any one of SEQ ID NO:1 from nucleotides 15-1652, SEQ ID NO:3 from nucleotides 15-1640,

SEQ ID NO:5 from nucleotides 15-1649, or SEQ ID NO:7 from nucleotides 15-1652 or a complement thereof.

6. An isolated nucleic acid molecule encoding Hsp60 comprising a nucleic acid sequence that encodes a polypeptide comprising any one of SEQ ID NOS: 2, 4, 6 or 8 or a variant Hsp60 that is at least 95% homologous to a polypeptide according to any one of SEQ ID NOS: 2, 4, 6 or 8.

7. An isolated nucleic acid molecule according to claim 3, encoding a polypeptide that is able to be selectively bound by an antibody specific for a *Streptococcus pneumoniae* Hsp60 or a *Streptococcus pyogenes* Hsp60.

8. An isolated nucleic acid molecule encoding at least 8 amino acids of a Streptococcal Hsp60 polypeptide selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-541 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, wherein the encoded Streptococcal Hsp60 polypeptide is able to bind to a major histocompatibility complex.

9. An isolated *Streptococcus pneumoniae* Hsp60 polypeptide.

10. An isolated *Streptococcus pyogenes* Hsp60 polypeptide.

11. An isolated Hsp60 polypeptide comprising the amino acid sequence of any one of a Streptococcal Hsp60 polypeptide selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-541 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, or variants thereof, wherein the polypeptide is able to be selectively bound by an antibody specific for either a *Streptococcus pneumoniae* Hsp60 and/or *Streptococcus pyogenes* Hsp60.

12. The isolated Hsp60 polypeptide according to any one of claims 9-11, wherein the Hsp60 polypeptide is fused to an additional polypeptide to create a fusion protein.

13. An isolated Hsp60 polypeptide comprising at least 8 amino acids selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-541 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, wherein the Hsp60 polypeptide is capable of binding to a major histocompatibility complex and eliciting or enhancing an immune response to *Streptococcus* in a human being.

14. The isolated Hsp60 polypeptide according to claim 11 wherein the polypeptide is derived from proteolytic cleavage.

15. The isolated Hsp60 polypeptide according to claim 11 wherein the polypeptide is derived from chemical synthesis.

16. The isolated Hsp60 according to claim 11 wherein the Hsp60 is an expression product of a transformed host cell containing a nucleic acid molecule encoding the Hsp60 or portion thereof.

17. The isolated Hsp60 polypeptide according to claim 11 wherein the polypeptide comprises greater than 95% homology to any one of a Streptococcal Hsp60 polypeptide selected from amino acid residues 1-545 of SEQ ID NO:2, amino acid residues 1-5410 of SEQ ID NO:4, amino acid residues 1-544 of SEQ ID NO:6, and amino acid residues 1-545 of SEQ ID NO:8, and wherein the Hsp60 polypeptide is able to be selectively bound by an antibody specific for either a *Streptococcus pneumoniae* Hsp60 or *Streptococcus pyogenes* Hsp60 or both.

18. An isolated polypeptide wherein the polypeptide is an expression product of a transformed host cell containing the nucleic acid molecule of any one of claims 1-8.

19. A vector comprising an isolated nucleic acid molecule according to any one of claims 1-8.

20. The vector according to claim 19 wherein the vector is an expression vector comprising a promoter in operative linkage with the isolated nucleic acid molecule encoding the Hsp60 or portion thereof.

21. The vector according to claim 20, further comprising a selectable or identifiable marker.

22. The vector according to claim 20 wherein the promoter is a constitutive or an inducible promoter.

23. A host cell containing a vector according to claim 19.

24. The host cell according to claim 23 wherein the host cell is selected from the group consisting of a bacterial cell, a mammalian cell, a yeast cell and an insect cell.

25. A composition comprising an Hsp60 polypeptide of any one of claims 9-16 in combination with a pharmaceutically acceptable carrier or diluent.

26. The composition according to claim 25 wherein the composition is suitable for systemic administration.

27. The composition according to claim 25 wherein the composition is suitable for oral administration.

28. The composition according to claim 25 wherein the composition is suitable for parenteral administration.

29. A method for eliciting or enhancing an immune response in a mammal against *Streptococcus*, comprising administering to the mammal an effective amount of an Hsp60 polypeptide according to any one of claims 9-16 in combination with a pharmaceutically acceptable carrier or diluent.

30. A method for eliciting or enhancing an immune response in a mammal against a target antigen comprising administering to the mammal the target antigen joined to an Hsp60 polypeptide according to any one of claims 9-16 in combination with a pharmaceutically acceptable carrier or diluent.

31. A composition comprising an isolated nucleic acid molecule of any one of claims 1-8 wherein the isolated nucleic acid molecule encodes a polypeptide having at least one amino acid difference from a corresponding polypeptide of an Hsp60 protein from an organism other than *Streptococcus*.

S. pneumoniae Hsp60-1 gene (SEQ ID NOS:1 and 2)

GAATTCGGCT TCAT ATG GCG GCT AAA GAC GTA AAA TTC GGT AAC GAC GCT CGT GTG AAA ATG CTG CGC GGC GTA AAC	77
Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala Arg Val Lys Met Leu Arg Gly Val Asn	21
GTA CTG GCA GAT GCA GTG AAA GTT ACC CTC GGC CCA AAA GGC CGT AAC GTA GTT CTG GAT AAA TCT TTC GGT GCA	152
Val Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe Gly Ala	46
CCG ACC ATC ACT AAA GAT GGT GTT TCC GTA GCA CGT GAA ATC GAA CTG GAA GAC AAG TTC GAA AAC ATG GGT GCG	227
Pro Thr Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile Glu Leu Glu Asp Lys Phe Glu Asn Met Gly Ala	71
CAG ATG GTG AAA GAA GTT GCC TCT AAA GCG AAC GAC GCT GCA GGT GAC GGT ACC ACC GCA ACC GTA CTG GCT	302
Gln Met Val Lys Glu Val Ala Ser Lys Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala	96
CAG TCC ATC ATC ACT GAA GGC CTG AAA GCC GTT GCT GCG ATG AAC CCG ATG GAT CTG AAA CGT GGT ATC GAC	377
Gln Ser Ile Ile Thr Glu Gly Leu Lys Ala Val Ala Ala Gly Met Asn Pro Met Asp Leu Lys Arg Gly Ile Asp	121
AAA GCT GTC GCT GCT GTT GAA GAA CTG AAA GCA CTG TCC GTA CCG TGC TCC GAC TCT AAA GCT ATT GCT CAG	452
Lys Ala Val Ala Ala Val Glu Glu Leu Lys Ala Leu Ser Val Pro Cys Ser Asp Ser Lys Ala Ile Ala Gln	146
GTT GGT ACC ATC TCC GCT AAC TCC GAC GAA ACC GTA GGT AAA CTG ATC GCT GAA GCG ATG GAC AAA GTC GGT AAA	527
Val Gly Thr Ile Ser Ala Asn Ser Asp Glu Thr Val Gly Lys Leu Ile Ala Glu Ala Met Asp Lys Val Gly Lys	171
GAA GGC GTG ATC ACC GTT GAA GAC GGT ACC CTG CAG GAC GAA CTG GAC GTG GTT GAA GGT ATG CAG TTC GAC	602
Glu Gly Val Ile Thr Val Glu Asp Gly Thr Gly Leu Gln Asp Glu Leu Asp Val Val Glu Gly Met Gln Phe Asp	196
CGT GGC TAC CTG TCT CCT TAC TTC ATC AAC AAG CCG GAA ACT GGC GCA GTA GAA TTG GAA AGC CCG TTC ATC CTG	677
Arg Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Lys Pro Glu Thr Gly Ala Val Glu Leu Gln Ser Pro Phe Ile Leu	221
CTG GCT GAC AAG AAA ATC TCC AAC ATC CGC GAA ATG CTG CCG GTT CTG GAA GCT GTA GCG AAA GCA GGC AAA CCG	752
Leu Ala Asp Lys Ile Ser Asn Ile Arg Glu Met Leu Pro Val Leu Glu Ala Val Ala Lys Ala Gly Lys Pro	246
CTG CTG ATC ATC GCT GAA GAT GTT GAA GGC GAA GCG CTG GCA ACT CTG GTT AAC ACC ATG CGC GGT ATC GTA	827
Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala Leu Ala Thr Leu Val Val Asn Thr Met Arg Gly Ile Val	271
AAA GTC GCT GCG GTT AAA GCA CCT GGC TTC GGC GAT CGT CGT AAA GCA ATG CTG CAG GAT ATC GCT ACC CTG ACC	902
Lys Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln Asp Ile Ala Thr Leu Thr	296
GGT GGT ACC GTT ATC TCT GAA GAG ATC GGT ATG GAG CTG GAA AAA GCA ACT CTG GAA GAT CTG GGC CAG GCG AAA	977
Gly Gly Thr Val Ile Ser Glu Glu Ile Gly Met Glu Leu Glu Lys Ala Thr Leu Glu Asp Leu Gly Gln Ala Lys	321
CGC GTT ATC AAC AAA GAT ACC ACC ATC GAT GGC GTG GGC GAC GAA GCT GCA ATC CAG GGT CGC GTG	1052
Arg Val Val Ile Asn Lys Asp Thr Thr Ile Asp Gly Val Gly Asp Glu Ala Ala Ile Gln Gly Arg Val	346

Fig. 1A

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2/22

ACT CAG ATT CGT CAG CAG ATC GAA GAA GCA ACT TCC GAC TAT GAC CGT GAA AAA CTG CAG GAG CGC GTA GCG AAA 1127
 Thr Gln Ile Arg Gln Gln Ile Glu Glu Ala Thr Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Val Ala Lys 371

 CTG GCA GGC GGC GTT GCG GTT ATC AAA GTT GGT GCT GCG ACT GAA GAA GTT GAA ATG AAA GAG AAG AAA GCC CGC GTT 1202
 Leu Ala Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu Val Glu Met Lys Glu Lys Ala Arg Val 396

 GAA GAT GCC CTG CAC CGT GCT GCG GTA GAA GAA GGC GTG GTT GCT GGT GGC GTT GCG CTG ATT CGC 1277
 Glu Asp Ala Leu His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val Ala Gly Gly Val Ala Leu Ile Arg 421

 GTA GCG TCT AAA ATT GCC GGC CTG AAA GGT CAG AAC GAA GAC CAG AAC GTA GGT ATC AAA GTT GCG CTG CGC GCA 1352
 Val Ala Ser Lys Ile Ala Gly Leu Lys Gly Gln Asn Glu Asp Gln Asn Val Gly Ile Lys Val Ala Leu Arg Ala 446

 ATG GAA TCC CCA CTG CGT CAA ATC GTA CTG AAC TGC GGC GAA GAG CCG TCT GTA GTG GCT AAC ACC GTG AAA GCC 1427
 Met Glu Ser Pro Leu Arg Gln Ile Val Leu Asn Cys Gly Glu Pro Ser Val Val Ala Asn Thr Val Lys Ala 471

 GGT GAC GGT AAC TAC GGT TAC AAC GCT GCA ACT GAA GAA TAC GGC AAC ATG ATC GAC ATG GGT ATC CTG GAT CCA 1502
 Gly Asp Gly Asn Tyr Gly Tyr Asn Ala Ala Thr Glu Glu Tyr Gly Asn Met Ile Asp Met Gly Ile Leu Asp Pro 496

 ACC AAA GTA ACT CGT TCT GCT CTG CAG TAC GCG GCT TCT GTT GCG GGT CTG ATG ATC ACC ACC GAG TGC ATG GTT 1577
 Thr Lys Val Thr Arg Ser Ala Leu Gln Tyr Ala Ala Ser Val Ala Gly Leu Met Ile Thr Thr Glu Cys Met Val 521

 ACC GAC CTG CCG AAA GGC GAT GCA CCT GAC TTA GGT GCT GGT GGT ATG GGC GGC ATG GGC GGA ATG ATG TGA 1652
 Thr Asp Leu Pro Lys Gly Asp Ala Pro Asp Leu Gly Ala Ala Gly Met Gly Met Gly Met Met * 546

 TCAAGCC GAATTC 1663

Fig. 1B

3/22

S. pneumoniae Hsp60-2 gene (SEQ ID NOS:3 and 4)

GAATTCCGCT TCAT ATG GCA AAA GAA ATT AAA TTT TCA TCA GAT GCC CGT TCA GCT ATG GTC CGT GGT GTC GAT ATC	77
Met Ala Lys Glu Ile Lys Phe Ser Ser Asp Ala Arg Ser Ala Met Val Arg Gly Val Asp Ile	21
CTT GCA GAT ACT GTT AAA GTA ACT TTG GGA CCA AAA GGT CGC AAT GTC GTT GAA AAG TCA TTC GGT TCA CCC	152
Leu Ala Asp Thr Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys Ser Phe Gly Ser Pro	46
TTG ATT ACC AAT GAC GGT GTG ACT ATT GCC AAA GAA ATT GAA GAC CAT TTT GAA AAT ATG GGT GCC AAA	227
Leu Ile Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp His Phe Glu Asn Met Gly Ala Lys	71
TTG GTA TCA GAA GTA GCT TCA AAA ACC AAT GAT ATC GCA GGT GAT GGA ACT ACA ACT GCA ACT GTT TTG ACC CAA	302
Leu Val Ser Glu Val Ala Ser Lys Thr Asn Asp Ile Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Thr Gln	96
GCA ATC GTC CGT GAA GGA ATC AAA AAC GTC ACA GCA GGT GCA AAT CCA ATC GGT ATT CGT CGT GGG ATT GAA ACA	377
Ala Ile Val Arg Glu Gly Ile Lys Asn Val Thr Ala Gly Ala Asn Pro Ile Gly Ile Arg Arg Gly Ile Glu Thr	121
GCA GTT GCC GCA GCA GTT GAA GCT TTG AAA AAC AAC GTC ATC CCT GTT GCC AAT AAA GAA GCT ATC GCT CAA GTT	452
Ala Val Ala Ala Val Glu Ala Leu Lys Asn Val Ile Pro Val Ala Asn Lys Glu Ala Ile Ala Gln Val	146
GCA GCC GTA TCT TCT CGT TCT GAA AAA GTT GGT GAG TAC ATC TCT GAA GCA ATG GAA AAA GTT GGC AAA GAC GGT	527
Ala Ala Val Ser Ser Arg Ser Glu Lys Val Gly Glu Tyr Ile Ser Glu Ala Met Glu Lys Val Gly Lys Asp Gly	171
GTC ATC ACC ATC GAA GAG TCA CGT GGT ATG GAA ACA GAG CTT GAA GTC GTA GAA GGA ATG CAG TTT GAC CGT GGT	602
Val Ile Thr Ile Glu Glu Ser Arg Gly Met Glu Thr Glu Leu Glu Val Val Glu Gly Met Gln Phe Asp Arg Gly	196
TAC CTT TCA CAG TAC ATG GTG ACA GAT AGC GAA AAA ATG GTG GCT GAC CTT GAA AAT CCG TAC ATT TTG ATT ACA	677
Tyr Leu Ser Gln Tyr Met Val Thr Asp Ser Glu Lys Met Val Ala Asp Leu Glu Asn Pro Tyr Ile Leu Ile Thr	221
GAC AAG AAA ATT TCC AAT ATC CAA GAA ATC TTG CCA CTT TTG GAA AGC ATT CTC CAA AGC AAT CGT CCA CTC TTG	752
Asp Lys Ile Ser Asn Ile Gln Glu Ile Leu Pro Leu Leu Glu Ser Ile Leu Gln Ser Asn Arg Pro Leu Leu	246
ATT ATT GCG GAT GAT GTG GAT GGT GAG GCT CTT CCA ACT CTT GTT TTG AAC AAG ATT CGT GGA ACC TTC AAC GTC	827
Ile Ile Ala Asp Asp Val Asp Gly Glu Ala Leu Pro Thr Leu Val Leu Asn Lys Ile Arg Gly Thr Phe Asn Val	271
GTA GCA GTC AAG GCA CCT GGT TTT GGT GAC CGT CGC AAA GCC ATG CTT GAA GAT ATC GCC ATC TTA ACA GGC GGA	902
Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Glu Asp Ile Ala Ile Leu Thr Gly Gly	296
ACA GTT ATC ACA GAA GAC CTT GGT CTT GAG TTG AAA GAT GCG ACA ATT GAA GCT CTT GGT CAA GCA GCG AGA GTG	977
Thr Val Ile Thr Glu Asp Leu Gly Leu Leu Lys Asp Ala Thr Ile Glu Ala Leu Gly Gln Ala Ala Arg Val	321
ACC GTG GAC AAA GAT AGC ACG GTT ATT GTA GAA GGT GCA GGA AAT CCT GAA GCG ATT TCT CAC CGT GTT GCG GTT	1052
Thr Val Asp Lys Asp Ser Thr Val Ile Val Glu Gly Ala Gly Asn Pro Glu Ala Ile Ser His Arg Val Ala Val	346

Fig. 2A

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4/22

ATC AAG TCT CAA ATC GAA ACT ACA ACT TCT GAA TTT GAC CGT GAA AAA TTG CAA GAA CGC TTG GCC AAA TTG TCA 1127
 Ile Lys Ser Gln Ile Glu Thr Thr Ser Glu Phe Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu Ser 371

GGT GGT GTA GCG GTT ATT AAG GTC GGA GCC GCA ACT GAA ACT GAG TTG AAA GAA ATG AAA CTC CGC ATT GAA GAT 1202
 Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu Thr Glu Leu Lys Glu Met Lys Leu Arg Ile Glu Asp 396

GCC CTC AAC GCT ACT CGT GCA GCT GTT GAA GAA GGT ATT GTT GCA GGT GGT GGA ACA GCT CTT GCC AAT GTG ATT 1277
 Ala Leu Asn Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Thr Ala Leu Ala Asn Val Ile 421

CCA GCT GTT GCT ACC TTG GAA TTG ACA GGA GAT GAA GCA ACA GGA CGT AAT ATT GTT CTC CGT GCT TTG GAA GAA 1352
 Pro Ala Val Ala Thr Leu Glu Leu Thr Gly Asp Glu Ala Thr Gly Arg Asn Ile Val Leu Arg Ala Leu Glu Glu 446

CCT GTT CGT CAA ATT GCT CAC AAT GCA GGA TTT GAA GGA TCT ATC GTT ATC GAT CGT TTG AAA AAT GCT GAG CTT 1427
 Pro Val Arg Gln Ile Ala His Asn Ala Gly Phe Glu Gly Ser Ile Val Ile Asp Arg Leu Lys Asn Ala Glu Leu 471

GGT ATA GGA TTC AAC GCA GCA ACT GGC GAG TGG GTT AAC ATG ATT GAT CAA GGT ATC ATT GAT CCA GTT AAA GTG 1502
 Gly Ile Gly Phe Asn Ala Ala Thr Gly Glu Trp Val Asn Met Ile Asp Gln Gly Ile Ile Asp Pro Val Lys Val 496

AGT CGT TCA GCC CTA CAA AAT GCA GCA TCT GTA GCC AGC TTG ATT TTG ACA ACA GAA GCA GTC GTA GCC AAT AAA 1577
 Ser Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Leu Ile Leu Thr Thr Glu Ala Val Val Ala Asn Lys 521

CCA GAA CCA GTA GCC CCA GCT CCA GCA ATG GAT CCA AGT ATG ATG GGT GGA ATG GGC GGA TGA TCAAAGC CGAATTC 1654
 Pro Glu Pro Val Ala Pro Ala Pro Met Asp Pro Ser Met Met Gly Gly Met Gly Gly * 542

Fig. 2B

S. pyogenes Hsp60-1 gene (SEQ ID NOS: 5 and 6)

GAATTCGGCT TCAT ATG GCG GCT AAA GAT GTA AAA TTC GGT AAC GAC GCT CGT GTA AAA ATG CTC CGC GGC GTA AAC	77
Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala Arg Val Lys Met Leu Arg Gly Val Asn	21
GTA CTG GCA GCA GCA GTT AAA GTA ACC CTG GGC CCG AAA GGC CGT AAC GTA GTG CTG GAC AAA TCC TTC GGC GCG	152
Val Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe Gly Ala	46
CCA ACC ATC ACG AAA GAT GGT GTT TCT GTA GCA CGT GAA ATC GAG CTG GAA GAC AAG TTC GAA AAC ATG GGC GCG	227
Pro Thr Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile Glu Leu Glu Asp Lys Phe Glu Asn Met Gly Ala	71
CAG ATG GTG AAA GAA GTG GCC TCT AAA GCG AAC GAC GCT GCA GGC GAC GGT ACC ACC GCG ACC GTG CTG GCT	302
Gln Met Val Lys Glu Val Ala Ser Lys Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala	96
CAG GCT ATC ATC ACC GAA GGT CTG AAA GCC GTT GCT GCG ATG AAC CCA ATG GAT CTG AAA CGT GGT ATC GAC	377
Gln Ala Ile Ile Thr Glu Gly Leu Lys Ala Val Ala Ala Gly Met Asn Pro Met Asp Leu Lys Arg Gly Ile Asp	121
AAA GCT GTC GCG TCC GCT GTT GAA GAA CTG AAA GCG CTG TCC GTA CCG TGC TCT GAC TCT AAA GCC ATT GCT CAG	452
Lys Ala Val Ala Ser Ala Val Glu Glu Leu Lys Ala Leu Ser Val Pro Cys Ser Asp Ser Lys Ala Ile Ala Gln	146
GTA GGT ACC ATC TCC GCT AAC TCC GAC GAA ACC GTA GGT AAA CTG ATC GCG GAA GCG ATG GAT AAA GTC GGT AAA	527
Val Gly Thr Ile Ser Ala Asn Ser Asp Glu Thr Val Gly Lys Leu Ile Ala Glu Ala Met Asp Lys Val Gly Lys	171
GAA GGC GTG ATC ACC GTT GAA GAC GGT ACC GGT CTG GAA GAC GAA CTG GAC GTG GTT GAA GGT ATG CAG TTC GAC	602
Glu Gly Val Ile Thr Val Glu Asp Gly Thr Glu Leu Glu Asp Glu Leu Asp Val Val Glu Gly Met Gln Phe Asp	196
CGC GGT TAC CTG TCC CCA TAC TTC ATC AAC AAG CCA GAA ACT GGC GCT GTT GAG CTG GAA AGC CCG TTC ATC CTG	677
Arg Gly Tyr Leu Ser Pro Tyr Ile Asn Lys Pro Glu Thr Gly Ala Val Glu Leu Glu Ser Pro Phe Ile Leu	221
CTG GCT GAC AAG AAA ATC TCC AAC ATC CGC GAA ATG CTG CCA GTG CTG GAA GCC GTT GCG AAA GCA GGC AAA CCG	752
Leu Ala Asp Lys Ile Ser Asn Ile Arg Glu Met Leu Pro Val Leu Glu Ala Val Ala Lys Ala Gly Lys Pro	246
CTG GTT ATC ATT GCT GAA GAC GTT GAA GGC GAA GCG CTG GCG ACC CTG GTG GTT AAC ACC ATG CGT GGC ATC GTG	827
Leu Val Ile Ile Ala Glu Asp Val Glu Gly Glu Ala Leu Ala Thr Leu Val Val Asn Thr Met Arg Gly Ile Val	271
AAA GTG GCT GCG GTT AAA GCA CCT GGC TTC GGC GAC CGC CGT AAA GCG ATG CTG CAG GAT ATC GCT ACC CTG ACC	902
Lys Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln Asp Ile Ala Thr Leu Thr	296
GGC GGT ACC GTC ATC TCT GAA GAG ATC GGT ATG GAG CTG GAA AAA GCG ACC CTG GAA GAC CTG GGC CAG GCT AAA	977
Gly Gly Thr Val Ile Ser Glu Glu Ile Gly Met Glu Leu Glu Lys Ala Thr Leu Glu Asp Leu Gly Gln Ala Lys	321
CGT GTT GTG ATC AAC AAA GAC ACC ACC ATC GAT GGC GTG GGC GAC GAA GCG GCG ATT CAG GGC CGT GTT	1052
Arg Val Val Ile Asn Lys Asp Thr Thr Ile Ile Asp Gly Val Gly Asp Glu Ala Ala Ile Gln Gly Arg Val	346

Fig. 3A

SUBSTITUTE SHEET (RULE 26)

6/22

GGT CAG ATC CGT AAG CAG ATC GAA GAA GCC ACT TCC GAT TAC GAC CGT GAA AAA CTG CAG GAG CGC GTA GCG AAA 1127
 Gly Gln Ile Arg Lys Gln Ile Glu Glu Ala Thr Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Val Ala Lys 371

 CTG GCA GGC GGT GCG GTA ATC AAA GTC GGT GCT GCG ACT GAA GTT GAA ATG AAA GAG AAA AAA GCA CGC GTT 1202
 Leu Ala Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu Val Glu Met Lys Glu Lys Ala Arg Val 396

 GAC GAT GCC CTG CAC GCG ACC CGT GCT GCG GTA GAA GAA GGC GTG GTT GCT GGT GGT GTG GCG CTG GTG CGT 1277
 Asp Asp Ala Leu His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val Ala Gly Gly Val Ala Leu Val Arg 421

 GTT GCC GCG AAA CTG TCC GGC CTG ACT GCT CAG AAC GAA GAT CAG AAC GTG GGT ATC AAA GTT GCG CTG CGC GCA 1352
 Val Ala Ala Lys Leu Ser Gly Leu Thr Ala Gln Asn Glu Asp Gln Asn Val Gly Ile Lys Val Ala Leu Arg Ala 446

 ATG GAA GCT CCA CTG CGT CAG ATC GTG TCC AAC GCC GGT GAA GAG CCA TCT GTT GTG ACC AAC AAC GTG AAA GCA 1427
 Met Glu Ala Pro Leu Arg Gln Ile Val Ser Asn Ala Gly Glu Pro Ser Val Val Thr Asn Asn Val Lys Ala 471

 GGC GAA GGT AAC TAC GGT TAC AAC GCA GCA ACT GAA GAA TAC GGC AAC ATG ATC GAC TTC GGT ATC CTG GAT CCA 1502
 Gly Glu Gly Asn Tyr Gly Tyr Asn Ala Ala Thr Glu Glu Tyr Gly Asn Met Ile Asp Phe Gly Ile Leu Asp Pro 496

 ACC AAA GTG ACC CGT TCT GCT CTG CAG TAC GCG GCA TCT GTC GCT GGC CTG ATG ATC ACC ACC GAG TGC ATG GTG 1577
 Thr Lys Val Thr Arg Ser Ala Leu Gln Tyr Ala Ala Ser Val Ala Gly Leu Met Ile Thr Thr Glu Cys Met Val 521

 ACC GAC CTG CCT AAA GGC GAC GCA CCT GAC TTA GGT GCT GCA GGC ATG GGT GGG ATG GGC GGT ATG ATG TGA TCAA 1653
 Thr Asp Leu Pro Lys Gly Asp Ala Pro Asp Leu Gly Ala Ala Gly Met Gly Met Gly Met Met 545

 GCC GAATTC 1662

Fig. 3B

7/22

S. pyogenes Hsp60-2 gene (SEQ ID NOS: 7 and 8)

GAATTCGGCT TCAT ATG GCA AAA GAA ATC AAA TTT TCA GCA GAT GCG CGT GCT GCC ATG GTG CGC GGA GTT GAT ATG	77
Met Ala Lys Glu Ile Lys Phe Ser Ala Asp Ala Arg Ala Ala Met Val Arg Gly Val Asp Met	21
TTA GCA GAT ACC GTC AAA GTA ACG CTT GGT CCT AAA GGG CGC AAT GTT GTT CTT GAA AAA GCT TTT GGT TCT CCC	152
Leu Ala Asp Thr Val Lys Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys Ala Phe Gly Ser Pro	46
TTA ATT ACT AAT GAC GGG GTA ACC ATT GCT AAA GAG ATC GAA TTA GAA GAT CAT TTT GAA AAC ATG GGA GCA AAA	227
Leu Ile Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp His Phe Glu Asn Met Gly Ala Lys	71
TTG GTG TCT GAA GTG GCT TCT AAA ACC AAT GAT ATT GCT GGT GAT GGG ACG ACT ACT GCA ACA GTT TTG ACA CAA	302
Leu Val Ser Glu Val Ala Ser Lys Thr Asn Asp Ile Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Thr Glu	96
GCC ATT GTT CAT GAA GGA CTA AAA AAT GTG ACA GCA GGT GCT AAT CCA ATT GGT ATC CGT CGA GGC ATT GAA ACA	377
Ala Ile Val His Glu Gly Leu Lys Asn Val Thr Ala Gly Ala Asn Pro Ile Gly Ile Arg Arg Gly Ile Glu Thr	121
GCA ACA GCA ACA GCT GTT GAA GCC TTG AAA GCC ATT GCT CAA CCT GTA TCT GGC AAG GAA GCT ATT GCT CAG GTC	452
Ala Ala Thr Ala Val Glu Ala Leu Lys Ala Ile Ala Gln Pro Val Ser Gly Glu Ala Ile Ala Gln Val	146
GCT GCA GTA TCA TCA CGC TCT GAA AAA GTT GGA GAG TAT ATC TCA GAA GCT ATG GAG CGT GTG GGC AAC GAT GGT	527
Ala Ala Val Ser Ser Arg Ser Glu Lys Val Gly Glu Tyr Ile Ser Glu Ala Met Glu Arg Val Gly Asn Asp Gly	171
GTG ATT ACC ATC GAA GAA TCT CGA GGT ATG GAA ACA GAA CTT GAA GTG GTC GAA GGC ATG CAA TTT GAC CGT GGT	602
Val Ile Thr Ile Glu Glu Ser Arg Gly Met Glu Thr Glu Leu Glu Val Val Glu Gly Met Gln Phe Asp Arg Gly	196
TAC CTG TCT CAA TAC ATG GTC ACA GAC AAT GAA AAA ATG GTT GCA GAC CTT GAA AAC CCA TTT ATC TTA ATC ACG	677
Tyr Leu Ser Gln Tyr Met Val Thr Asp Asn Glu Lys Met Val Ala Asp Leu Glu Asn Pro Phe Ile Leu Ile Thr	221
GAT AAA AAA GTG TCA AAC ATC CAA GAC ATT TTG CCA CTA CTT GAG GAA GTT CTT AAA ACC AAC CGT CCA TTA CTC	752
Asp Lys Lys Val Ser Asn Ile Gln Asp Ile Leu Pro Leu Leu Glu Val Leu Lys Thr Asn Arg Pro Leu Leu	246
ATT ATT GCA GAT GAT GTG GAT GGT GAA GCA CTT CCA ACC CTT GTC TTG AAC AAG ATT CGT GGT ACT TTC AAT GTG	827
Ile Ile Ala Asp Asp Val Asp Gly Glu Ala Leu Pro Thr Leu Val Leu Asn Lys Ile Arg Gly Thr Phe Asn Val	271
GTT GCT GTC AAA GCG CCA GGA TTT GGT GAT CGT CGT AAA GCT ATG CTT GAA GAC ATT GCT ATC TTG ACA GGT GGT	902
Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Glu Asp Ile Ala Ile Leu Thr Gly Gly	296
ACA GTG ATT ACA GAG GAT CTA GGA CTT GAA TTA AAA GAT GCT ACA ATG ACA GCC CTT GGA CAG GCT GCT AAG ATT	977
Thr Val Ile Thr Glu Asp Leu Gly Leu Lys Asp Ala Thr Met Thr Ala Leu Gly Gln Ala Ala Lys Ile	321
ACA GTT GAT AAA GAT AGC ACA GTA ATT GTT GAA GGT TCA GGA AGT TCA GAA GCT ATT GCT AAC CGT ATT GCA CTG	1052
Thr Val Asp Lys Asp Ser Thr Val Ile Val Glu Gly Ser Ser Glu Ala Ile Ala Asn Arg Ile Ala Leu	346

Fig. 4A

SUBSTITUTE SHEET (RULE 26)

8/22

ATT AAA TCG CAA TTA GAA ACA ACA ACT TCT GAC CGT GAA AAA CTA CAA GAA CGT TTG GCG AAA TTA GCT 1127
 Ile Lys Ser Gln Leu Glu Thr Thr Ser Asp Phe Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu Ala 371

GGT GGT GTA GCT GTT ATC AAA GTA GGA GCT CCA ACA GAG ACA GCT TTA AAA GAA ATG AAA CTT CGC ATT GAG GAT 1202
 Gly Gly Val Ala Val Ile Lys Val Gly Ala Pro Thr Ala Leu Lys Glu Met Lys Leu Arg Ile Glu Asp 396

GCT CTA AAT GCT ACA CGT GCA GCC GTT GAA GAA GGT ATC GTT GCT GGT GGA ACA GCA CTT ATT ACG GTT ATT 1277
 Ala Leu Asn Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Thr Ala Leu Ile Thr Val Ile 421

GAA AAA GTA GCA GCT CTT GAG CTT GAG GGC GAT GAT GCT ACT GGA CGT AAC ATT GTG CTT CGT GCT CTA GAA GAG 1352
 Glu Lys Val Ala Ala Leu Glu Leu Glu Gly Asp Asp Ala Thr Gly Arg Asn Ile Val Leu Arg Ala Leu Glu Glu 446

CCT GTA CGT CAA ATT GCT TTA AAT GCT GGG TAC GAA GGC TCC GTA GTT ATT GAC AAG TTG AAA AAC AGC CCT GCA 1427
 Pro Val Arg Gln Ile Ala Leu Asn Ala Gly Tyr Glu Gly Ser Val Val Ile Asp Lys Leu Lys Asn Ser Pro Ala 471

GGA ACA GGA TTT AAT GCT GCA ACA GGT GAG TGG GTT GAT ATG ATT AAA ACA GGA ATC ATT GAC CCT GTC AAA GTA 1502
 Gly Thr Gly Phe Asn Ala Ala Thr Gly Glu Trp Val Asp Met Ile Lys Thr Gly Ile Ile Asp Pro Val Lys Val 496

ACA CGA TCA GCG CTT CAA AAT GCA GCT TCT GTA GCT AGT CTT ATT TTG ACA ACA GAA GCA GTT GTT GCT AAT AAA 1577
 Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Leu Ile Leu Thr Thr Glu Ala Val Val Ala Asn Lys 521

CCT GAA CCA GCT ACG CCA GCG CCA GCA ATG CCA GCA GGT ATG GAT CCA GGA ATG ATG GGT GGG ATG GGC GGA TAA 1652
 Pro Glu Pro Ala Thr Pro Ala Pro Ala Met Pro Ala Gly Met Asp Pro Gly Met Met Gly Gly Met Gly Gly 546

GCCGAAT TC 1661

Fig. 4B

Sequencing strategy (scale: 1cm=approx. 100bp)

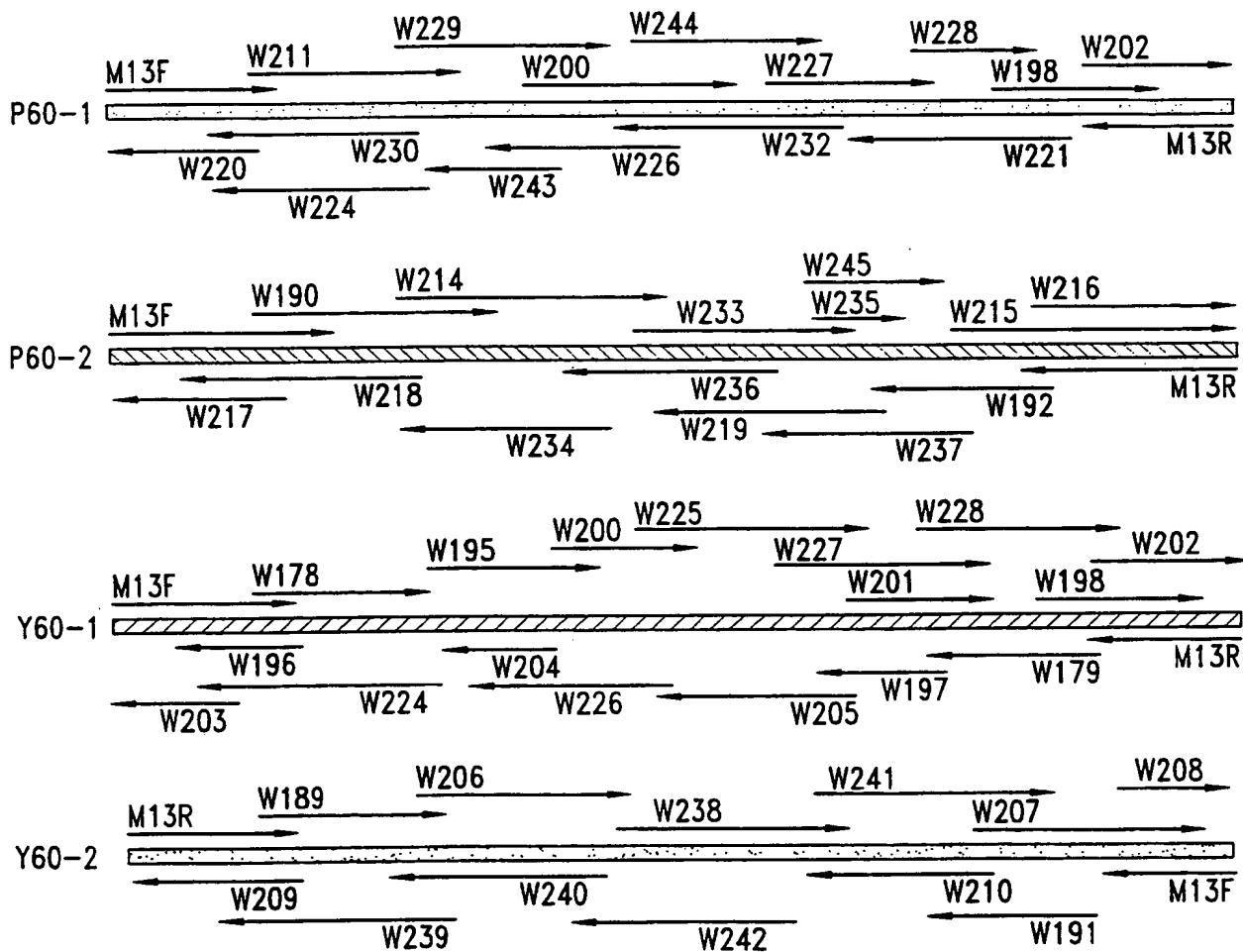


Fig. 5

10/22

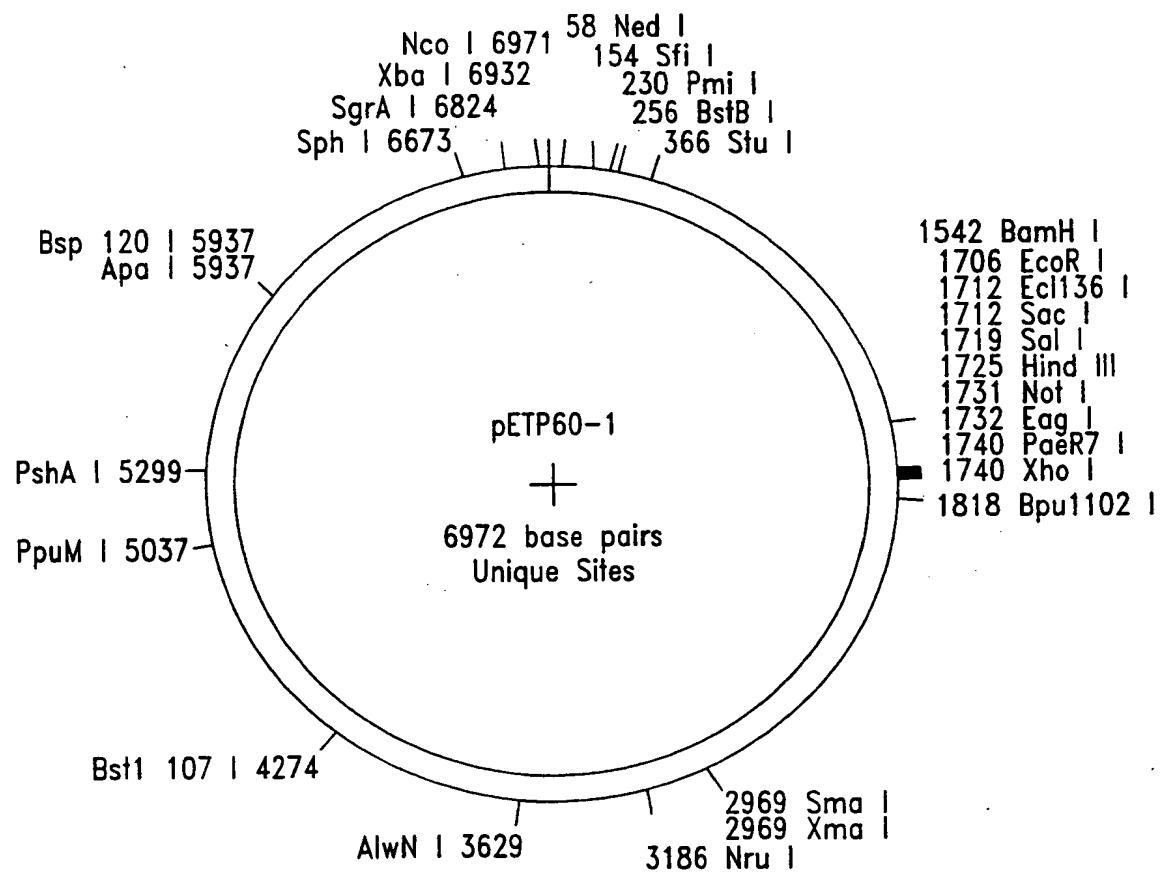


Fig. 6

11/22

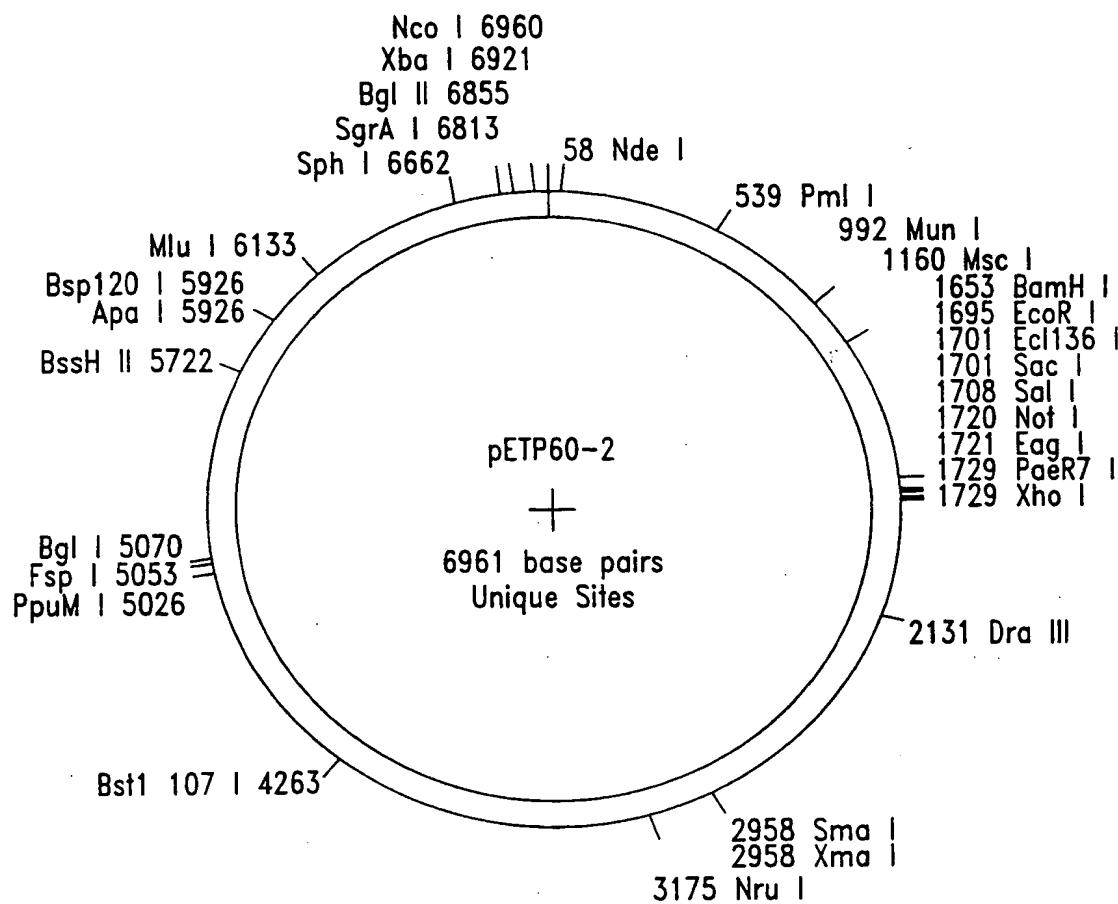


Fig. 7

12/22

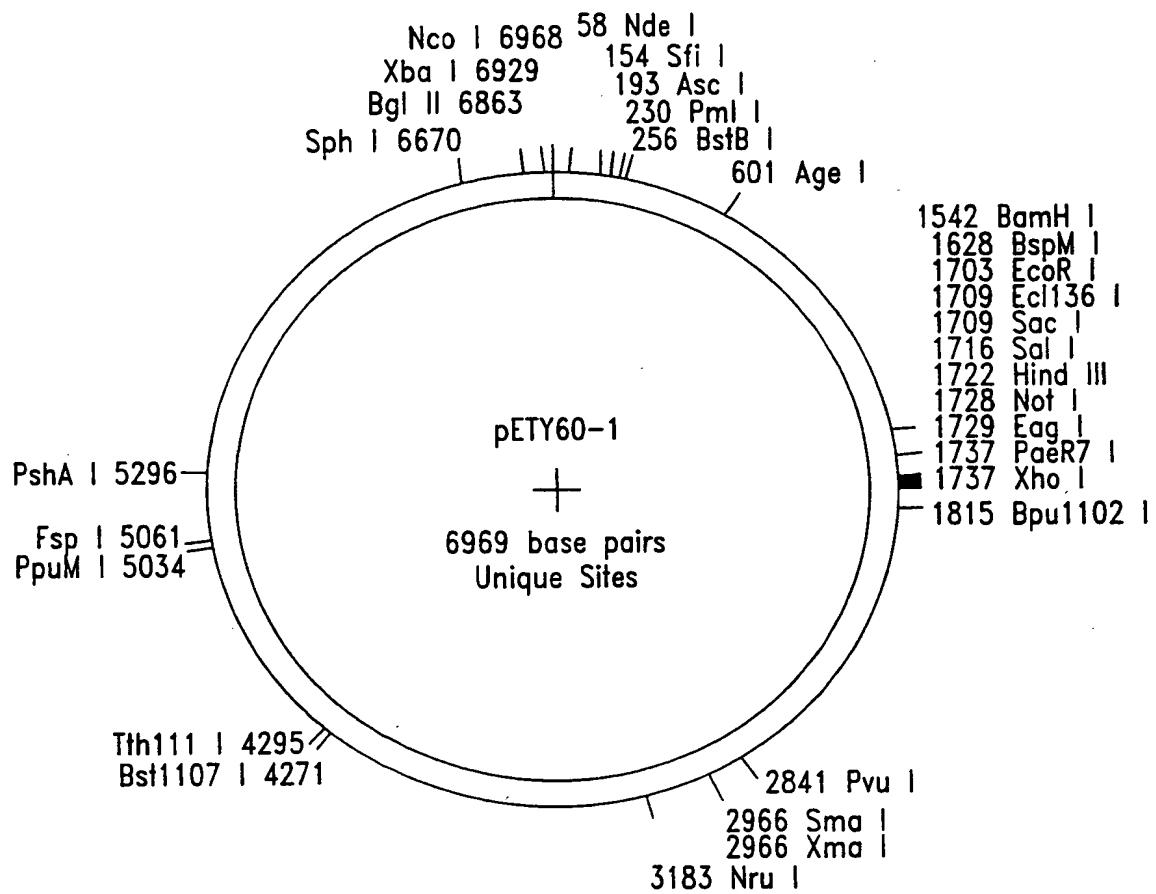


Fig. 8

13/22

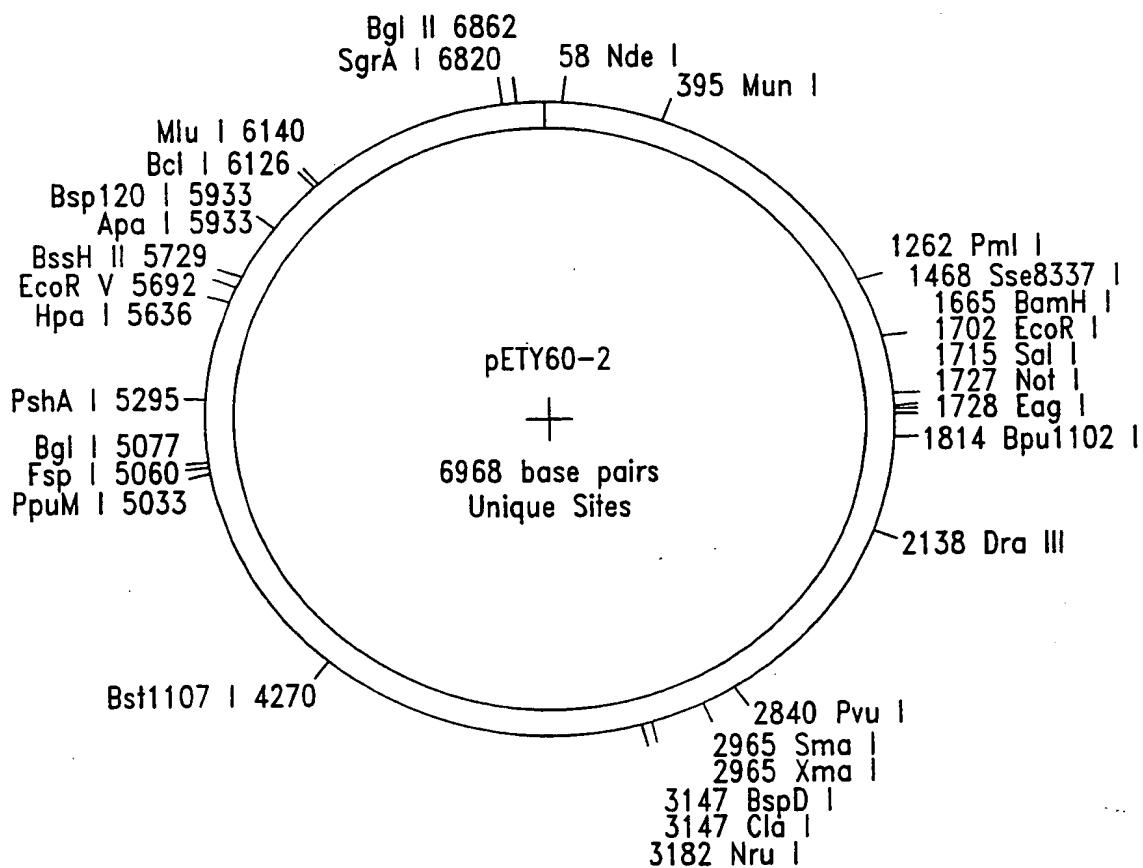
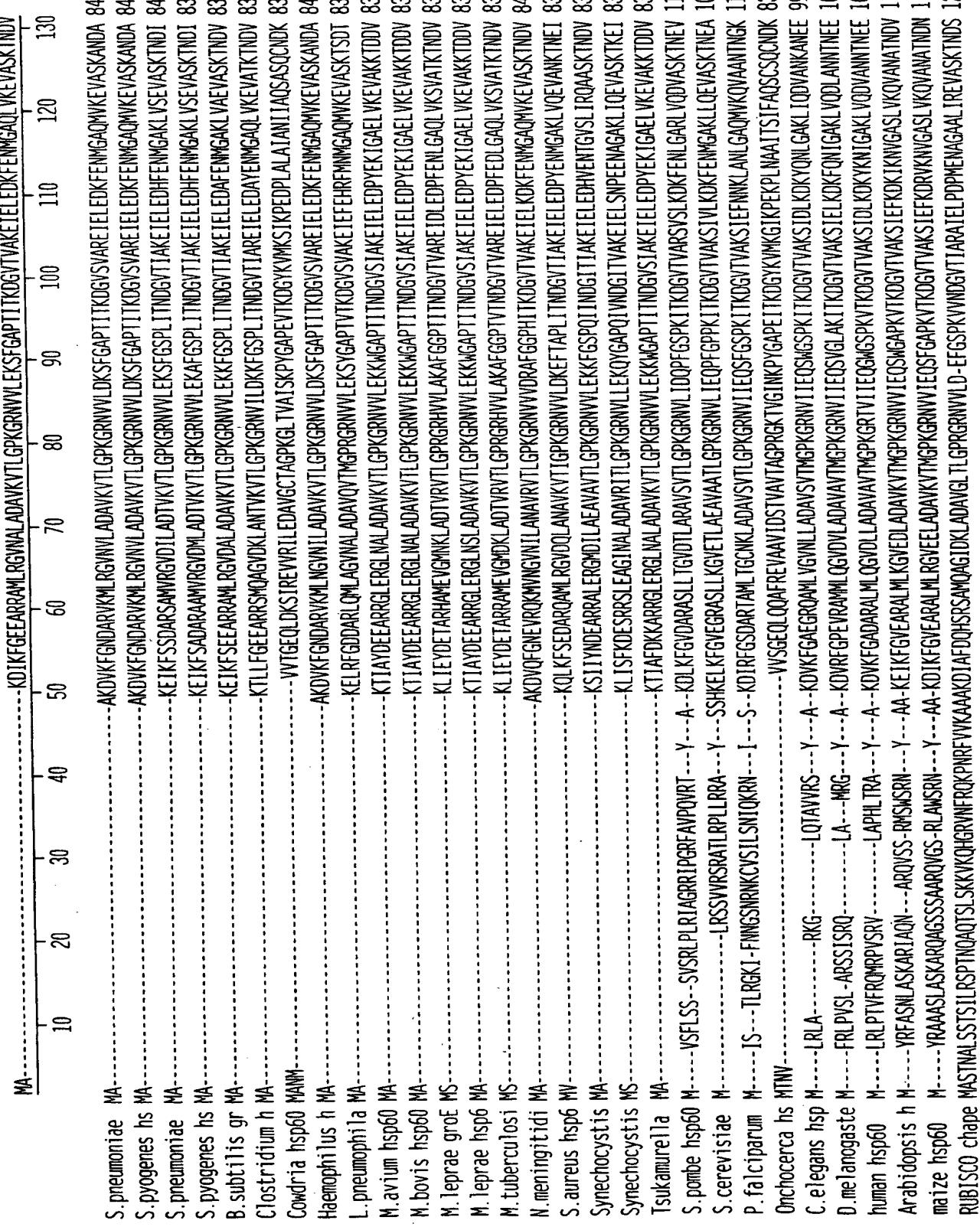


Fig. 9

14/22

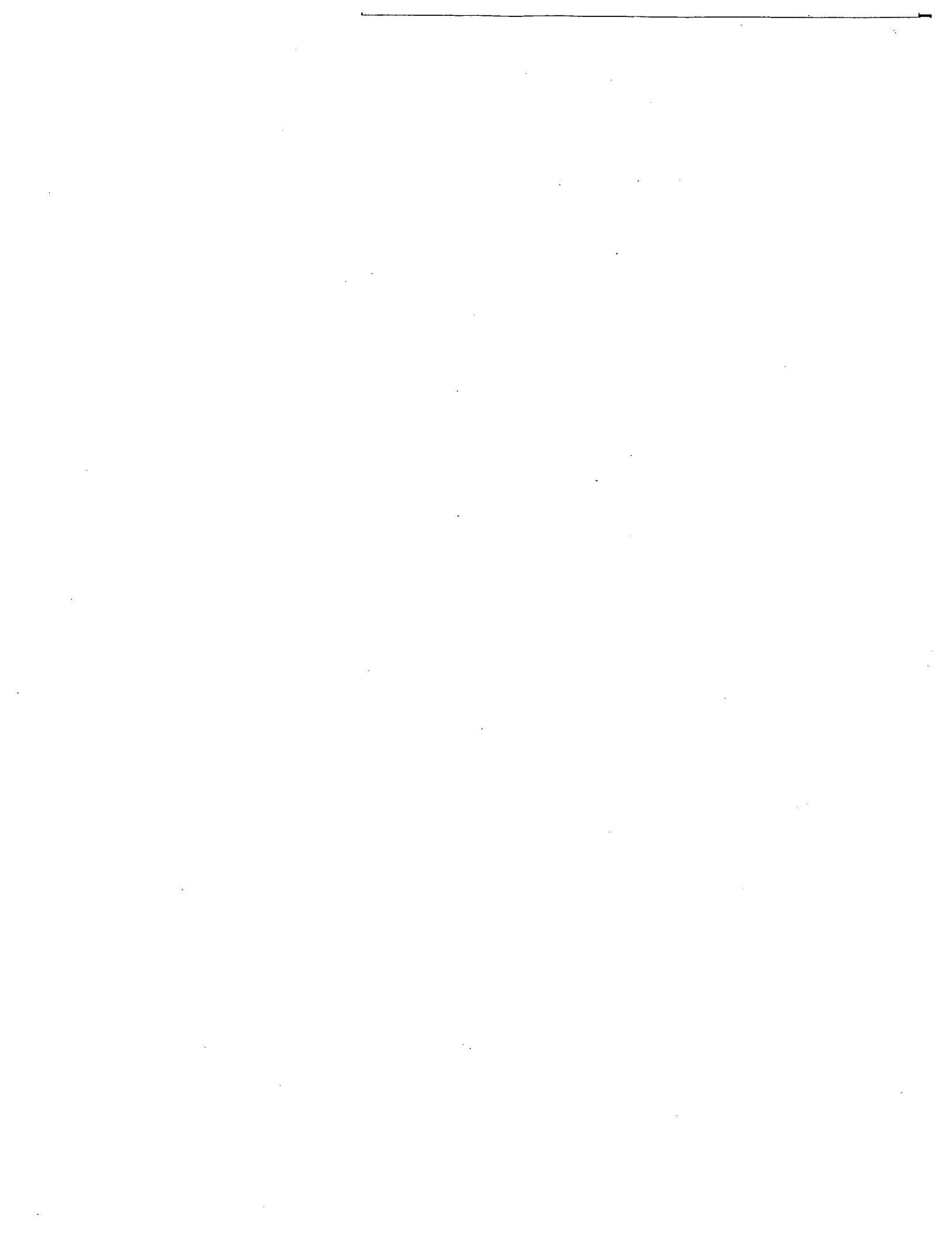


	140	150	160	170	180	190	200	210	220	230	240	250	260
<i>S. pneumoniae</i>	AGGTTTATVLAQATIKEGLKNAVAGANPDLRGGTOKAVADWEELKAIAKPV--ETKEIJAQWATISANGDEEIGE--LIAEAMEKYGKEGVITV--EEKTLETELEWEG-MQFDRGYISPFV												
<i>S. pyogenes</i> hs	AGGTTTATVLAQATIKEGLKNAVAGANPDLRGGTOKAVADWEELKAIASVPC--SDSKAIAQNGTISANSDETEVK--LIAEAMDKVKGKEGVITV--EDGTGLODELWEG-MQFDRGYISPFV	205											
<i>S. pneumoniae</i>	AGGTTTATVLAQATIKEGLKNAVAGANPDLRGGTOKAVADWEELKAIASVPC--SDSKAIAQNGTISANSDETEVK--ANKEIAQAVAISS-RSEKIGE--YISEAMEKVGKGVITI--EESRGMTTELEWEG-MQFDRGYISOMW	203											
<i>S. pyogenes</i> hs	AGGTTTATVLAQATIKEGLKNAVAGANPDLRGGTOKAVADWEELKAIASVPC--SGKEIAQAVAISS-RSEKIGE--YISEAMEKVGKGVITI--EESRGMTTELEWEG-MQFDRGYISOMW	203											
<i>B. subtilis</i> gr	AGGTTTATVLAQAMIREGLKNTAGANPVGKMGDAVAVAIENKEISKP1--EGKESIAQVAIASS-ADEEVGS--LIAEAMERIGNDGVITI--EESKGFTTELEWEG-MQFDRGYISAPW	203											
<i>Clostridium</i> h	AGGTTTATVLAQATIREGLKNTAGANPILTRIGIKAETKAVEELOKISKPV--NGKEDIAVVAIASS-ADEEVGS--LIAEAMERIGNDGVITI--EESKGFTTELEWEG-MQFDRGYISAMW	203											
<i>Cowdria</i> hsp60	VGDDTTTCAITVLAQATIYNEGLKNAVAGANPDLRGGTOKAVADWEELKOMREVSE--EEJAQWATISANGKNTGK--IAQCKEVKGKGVITVEESKGKEL--DVEKTD-MQFDRGYISPFV	205											
<i>Haemophilus</i> h	AGGTTTATVLAQATIYNEGLKNAVAGANPDLRGGTOKAVADWEELKOMSKPC--ETSKIEQDGTISANSISIWGQ--LIAQAMEKVGKEGVITV--EDGTGLODELWEG-MQFDRGYISPFV	205											
<i>L. pneumophila</i>	AGGTTTATVLAQATIYNEGLKNAVAGANPDLRGGTOKAVADWEELKOMSKPC--KDSKAIJAQGTTISANSDEAIGA--LIAEAMERIGNDGVITI--EDGNGLENELSWEG-MQFDRGYISPFV	204											
<i>M. avium</i> hsp60	AGGTTTATVLAQATIYNEGLKNAVAGANPDLRGGTOKAVADWEELKOMSKPC--ETKDQIAATAAISAS-GD01GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>M. bovis</i> hsp60	AGGTTTATVLAQATIYNEGLKNAVAGANPDLRGGTOKAVADWEELKOMSKPC--ETKEQIAATAAISAS-GD02GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>M. leprae</i> groe	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKEQIAATAAISAS-GD03GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>M. leprae</i> hsp6	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKEQIAATAAISAS-GD04GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>M. tuberculosis</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKEQIAATAAISAS-GD05GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>N. meningitidis</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ENKEIAQGATISAGNDENVGQ--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>S. aureus</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKQDQIAATAGISA-GD06GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	204											
<i>Synechocystis</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKQDQIAATAGISA-GD07GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>Tsukamure</i> 1a	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKQDQIAATAGISA-GD08GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>S. pombe</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKQDQIAATAGISA-GD09GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>S. cerevisiae</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKQDQIAATAGISA-GD10GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>P. falciparum</i>	AGGTTTATVLAQALVREGLRNVAAGANPGLKRGTEKAVDVKVETTLLKDAKEV--ETKQDQIAATAGISA-GD11GD--LIAEAMERIGNDGVITI--EESNTFGLQLETEG-MRFDGQYISGFV	203											
<i>Onchocerca</i> hs	VGGTTTCSITLTSQMTVEASKTASAGDRTISKGHQKADWKEVASHARTSLSKIDEVAQWATISANGDRTGSN--JADAWKVKVGKGVITV--EVELITG-MQFDRGYISPFV	207											
<i>C. elegans</i> hsp	AGDGTTCATVLTAAKEGFEKISGGNPAVTRGGMNLAVETKVNKLTKNSRPY--TPEEIAQWATISANGDRTGSN--LISDAWKKVGKGVITV--KOGKTLNDLEI1EG-MKFDRGYISPFV	220											
<i>D. melanogaster</i>	AGDGTTCATVLTAAKEGFEKISGGNPAVTRGGMNLAVETKVNKLTKNSRPY--TPEEIAQWATISANGDRTGSN--LISDAWKKVGKGVITV--KOGKTLNDLEI1EG-MKFDRGYISPFV	229											
<i>human</i> hsp60	AGDGTTCATVLTAAKEGFEKISGGNPAVTRGGMNLAVETKVNKLTKNSRPY--TPEEIAQWATISANGDRTGSN--LISDAWKKVGKGVITV--KOGKTLNDLEI1EG-MKFDRGYISPFV	229											
<i>Arabidopsis</i> h	AGDGTTCATVLTAAKEGFEKISGGNPAVTRGGMNLAVETKVNKLTKNSRPY--TPEEIAQWATISANGDRTGSN--LISDAWKKVGKGVITV--KOGKTLNDLEI1EG-MKFDRGYISPFV	235											
<i>maize</i> hsp60	AGDGTTCATVLTAAKEGFEKISGGNPAVTRGGMNLAVETKVNKLTKNSRPY--TPEEIAQWATISANGDRTGSN--LISDAWKKVGKGVITV--KOGKTLNDLEI1EG-MKFDRGYISPFV	238											
<i>RUBISCO</i> chaperone	AGDGTTCATVLTAAKEGFEKISGGNPAVTRGGMNLAVETKVNKLTKNSRPY--TPEEIAQWATISANGDRTGSN--LISDAWKKVGKGVITV--KOGKTLNDLEI1EG-MKFDRGYISPFV	250											

TSEOKAELLEDPILLTDKKSNIQDILLPYLEEVA		-QAGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGSLSEDATLED-LGQAKRWWVTKDOTT		331	
S. pneumoniae	NKPEGAELESPILLADKKISNIRELPYLEEVA	-KAGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGMELEKATLED-LGQAKRWWVTKDOTT	331		
S. pyogenes	NKPEGAELESPILLADKKISNIRELPYLEEVA	-KAGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGMELEKATLED-LGQAKRWWVTKDOTT	331		
S. pneumoniae	TDSEKWADELNPILITDKKSNIQDILLPYLEEVL	--QSNRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
S. pyogenes	TDNEKWADELNPILITDKKSNIQDILLPYLEEVL	--KTRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
B. subtilis	QAGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	--QGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
Clostridium	QDTEKMEAWDNPVLTIDKKISNIQDILLPYLEQIV	--QAGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
Cowdria	hsp60	TNSEKMLVEENPVTTEKKLNITQPLPITLENIA	--RSGRPLLIADVEGEALSTVLNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
Haemophilus	h	NKPEATVLEDNPFTLWKKISNIRELPYLEGVA	--KAGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
L. pneumophila	LNQDQMSCELEHPILLVYKVKSSIRELPYLEGVA	--KSGRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
M. avium	hsp60	TDAEQRCAVLEDPTLVSSKVKSTVKKPLLEKVI	--QAGKPLLIADVEGEALSTLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
M. bovis	hsp60	TDPERCAVLEDPTLVSSKVKSTVKKPLLEKVI	--GAGKPLLIADVEGEALSTLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
M. leprae	groE	TDFDSQCAVLDPLVLLHQEKISSPELPMEKVI	--ESGRPLLIADVEGEALSTLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
M. leprae	hsp6	TDAEQRCAVLEPTLVSSKVKSTVKKPLLEKVI	--QAGKPLLIADVEGEALSTLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
M. tuberculosis	TDFDQCAVLEDALILHDKISSPLVPLLEKVA	--GTGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
N. meningitidis	NDAEQIAGLDNPFLDFKKISNIRODLPYLEQVA	--KASPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
S. aureus	hsp6	TDSOKWAELERPILITDKKSNIQDILLPYLEQIV	--QSNRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
S. cerevisiae	Tsukamurella	TDAEQRCAVLEDPTVKKPLLEKVI	--QSGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
S. pombe	hsp60	TDKSKVKEENPLLSEKKSVAQDILPSL	--ELAAQ-RPPLLIADVEGEALAACTMILRGLQWIAKAPGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
S. cerevisiae	TDPSSKVEEPLLSEKKSISQDILPAL	--EISNQS-RPPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
P. falciparum	NN-SQKVLEDKPYLTIEKKLNITQPLSILEAVW	--LONQSSVIAEDVGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
Ochococerca	h	TNNERKVELDQPLLTIEKKLNITQPLSILEAVW	--KSGKPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
C. elegans	hsp	TSAGKAKVEYEKAVLSEKKSISQDITPAL	--ELANKL-RPPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
D. melanogaster	hsp60	ISSKGAKVEFDDALLLSEKKSVAEHSPLASRTRKPLVIIAEDVGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		
human	hsp60	NTSKGKCEFFDAYILLSEKKLSSQDITPAL	--ELANAH-RPPLVIAEDVGEALSTVNLKVLQWIAKAPGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
Arabidopsis	h	TNQTKQCKELDPLLJHEKKISSINSIUKVL	--ELALKR-QRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
maize	hsp60	TNSKAKCCEPDPILLIHDKRTVTHHAWIKVL	--EMALKK-QRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322	
ribisco	chaperone	QIRPLLIADVEGEALATLVNKLRGTLYWAIAKGFDGRRKAMLQDIAITGGQVISEE-LGQAAKTTVKDOSTV	322		

SUBSTITUTE SHEET (RULE 26)

17/22



19/22

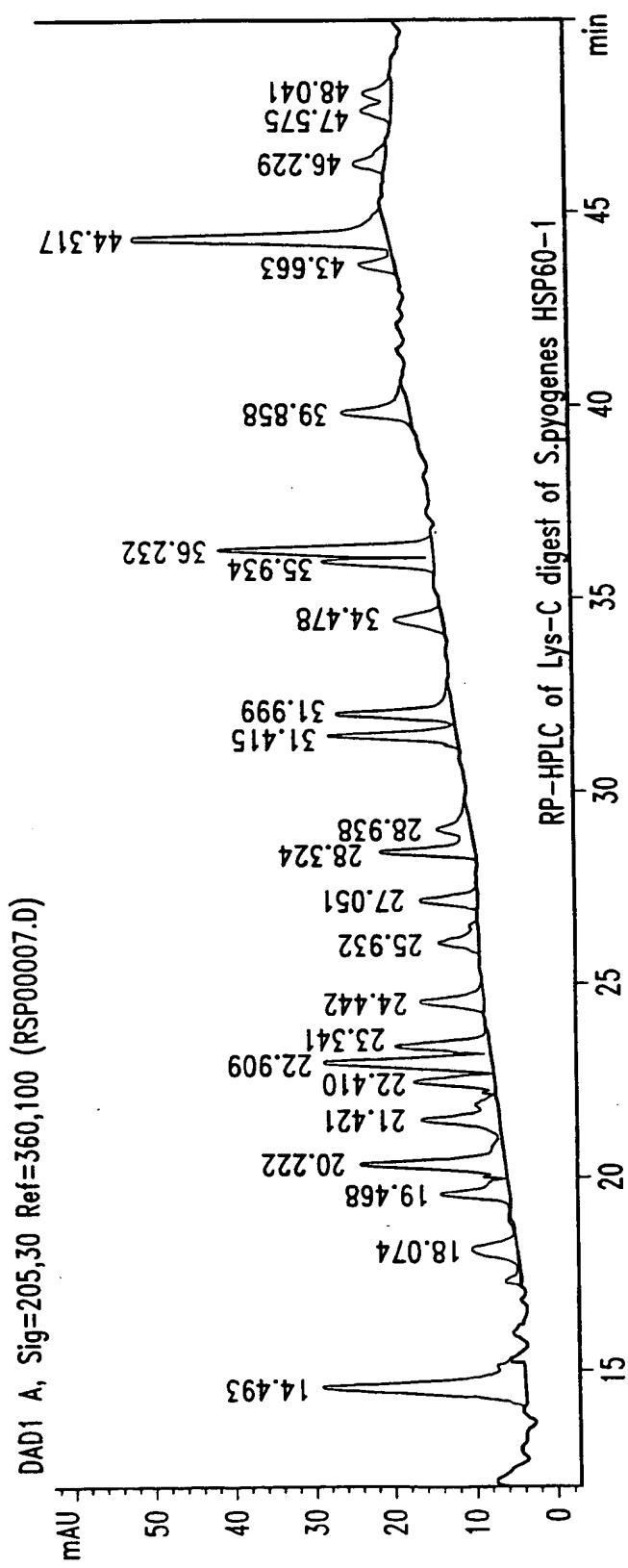


Fig. 11A

20/22

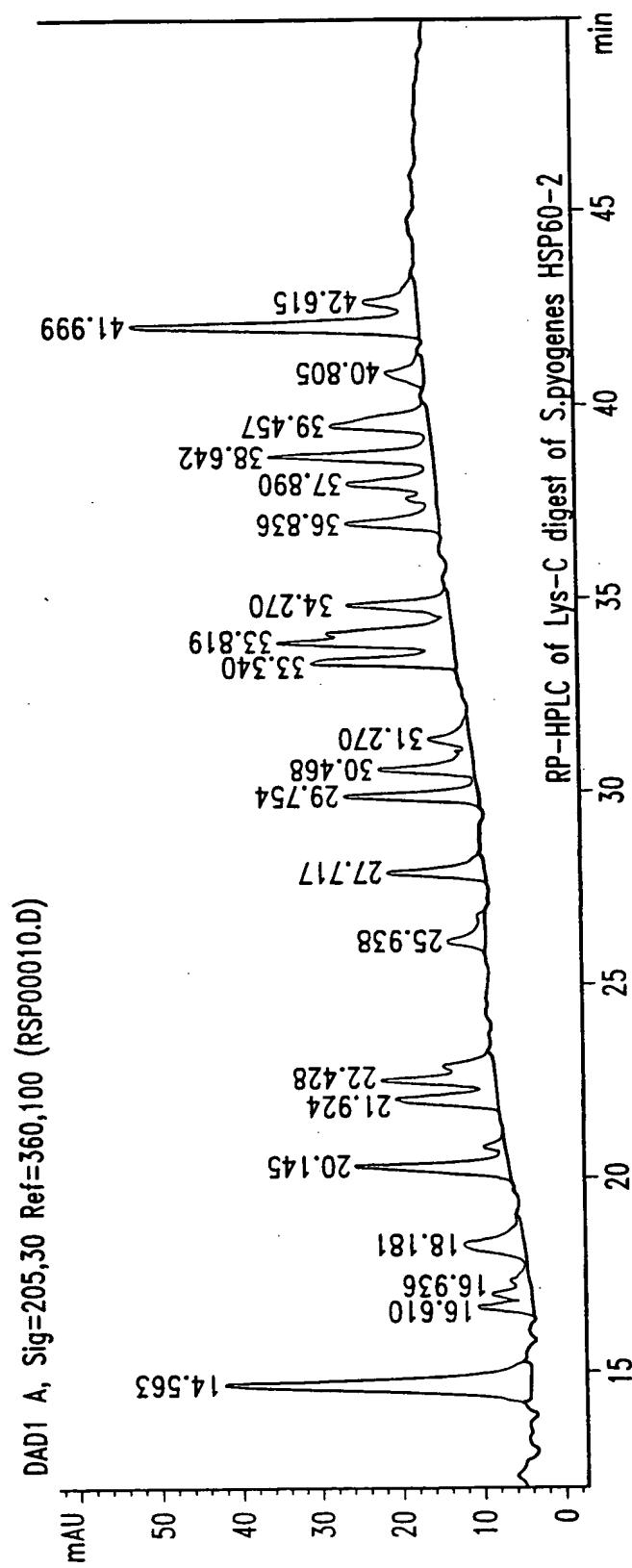


Fig. 11B

21/22

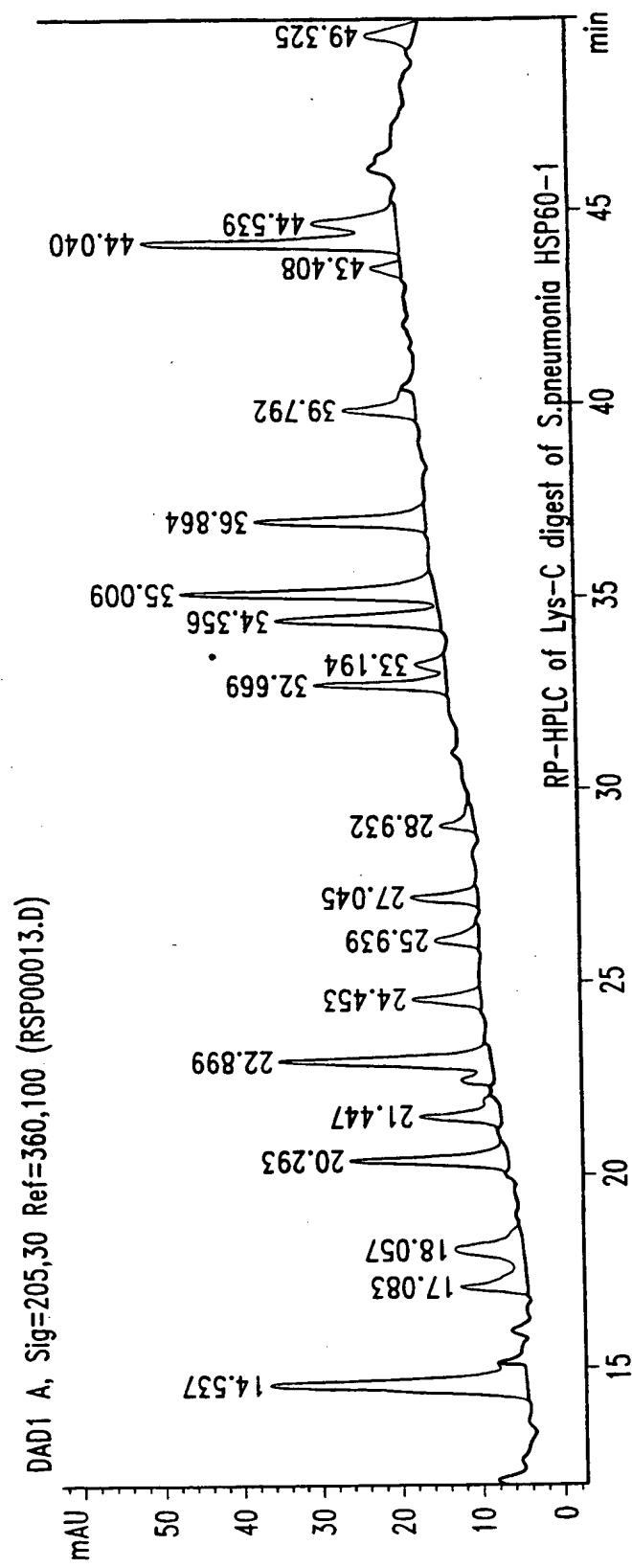


Fig. 11C

22/22

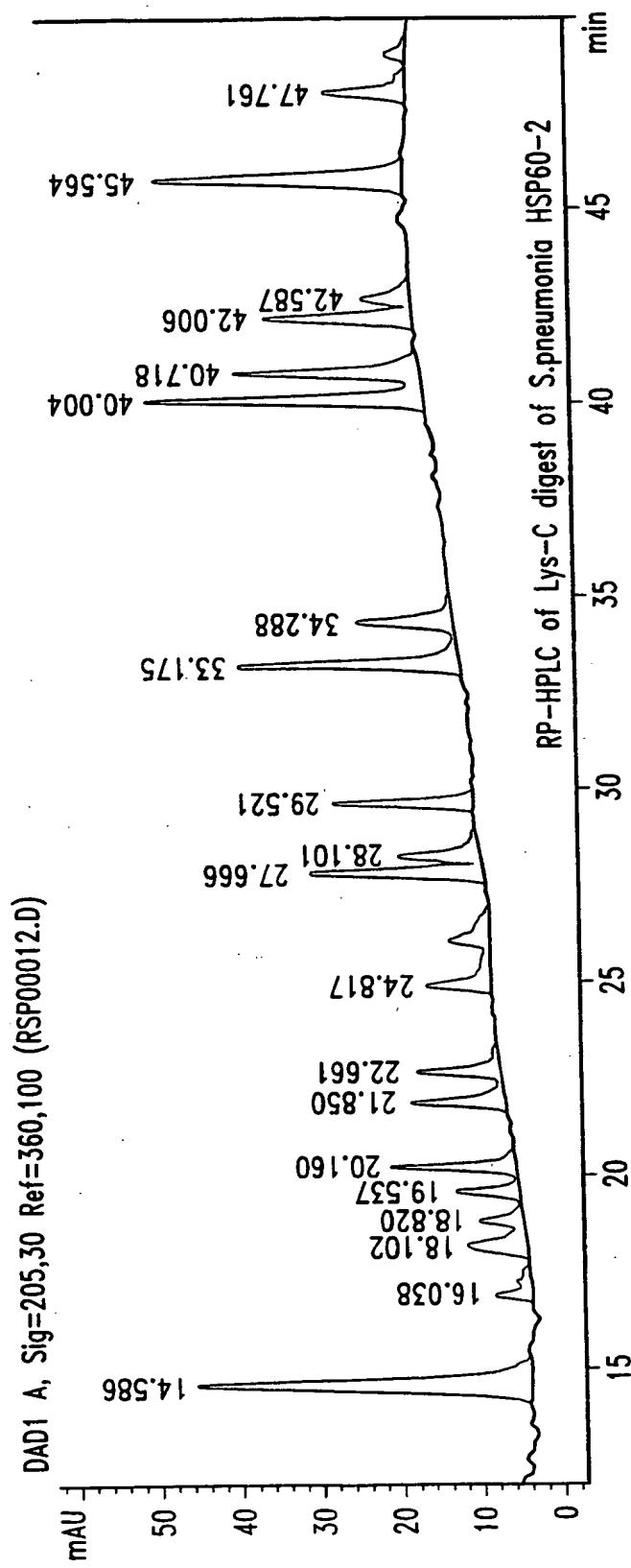


Fig. 11D

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Stessgen Biotechnologies Corporation
- (ii) TITLE OF INVENTION: STREPTOCOCCAL HEAT SHOCK PROTEINS OF THE HSP60 FAMILY
- (iii) NUMBER OF SEQUENCES: 91
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: Gowling, Strathy & Henderson
 - (B) STREET: Commerce Court West, Suite 4900
 - (C) CITY: Toronto
 - (D) STATE: Ontario
 - (E) COUNTRY: Canada
 - (F) ZIP: M5L 1J3
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE: 29 December 1998
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Omar A. Nassif
 - (B) REGISTRATION NUMBER: 4016
 - (C) REFERENCE/DOCKET NUMBER: T8464440WO
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: (416) 862-7525
 - (B) TELEFAX: (416) 862-7661

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1665 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 15..1649

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCGGCT TCAT ATG GCG GCT AAA GAC GTC AAA TTC GGT AAC GAC GCT	50
Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala	
1 5 10	
CGT GTG AAA ATG CTG CGC GGC GTA AAC GTA CTG GCA GAT GCA GTG AAA	98
Arg Val Lys Met Leu Arg Gly Val Asn Val Leu Ala Asp Ala Val Lys	
15 20 25	
GTT ACC CTC GGC CCA AAA GGC CGT AAC GTA GTT CTG GAT AAA TCT TTC	146
Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe	
30 35 40	
GGT GCA CCG ACC ATC ACT AAA GAT GGT GTT TCC GTA GCA CGT GAA ATC	194
Gly Ala Pro Thr Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile	
45 50 55 60	
GAA CTG GAA GAC AAG TTC GAA AAC ATG GGT GCG CAG ATG GTG AAA GAA	242
Glu Leu Glu Asp Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu	
65 70 75	
GTT GCC TCT AAA GCG AAC GAC GCT GCA GGT GAC GGT ACC ACC ACC GCA	290
Val Ala Ser Lys Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Ala	
80 85 90	
ACC GTA CTG GCT CAG TCC ATC ATC ACT GAA GGC CTG AAA GCC GTT GCT	338
Thr Val Leu Ala Gln Ser Ile Ile Thr Glu Gly Leu Lys Ala Val Ala	
95 100 105	
GCG GGC ATG AAC CCG ATG GAT CTG AAA CGT GGT ATC GAC AAA GCT GTC	386
Ala Gly Met Asn Pro Met Asp Leu Lys Arg Gly Ile Asp Lys Ala Val	
110 115 120	
GCT GCT GCT GTT GAA GAA CTG AAA GCA CTG TCC GTA CCG TGC TCC GAC	434
Ala Ala Ala Val Glu Glu Leu Lys Ala Leu Ser Val Pro Cys Ser Asp	
125 130 135 140	
TCT AAA GCT ATT GCT CAG GTT GGT ACC ATC TCC GCT AAC TCC GAC GAA	482
Ser Lys Ala Ile Ala Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Glu	
145 150 155	
ACC GTA GGT AAA CTG ATC GCT GAA GCG ATG GAC AAA GTC GGT AAA GAA	530
Thr Val Gly Lys Leu Ile Ala Glu Ala Met Asp Lys Val Gly Lys Glu	
160 165 170	
GGC GTG ATC ACC GTT GAA GAC GGT ACC GGT CTG CAG GAC GAA CTG GAC	578
Gly Val Ile Thr Val Glu Asp Gly Thr Gly Leu Gln Asp Glu Leu Asp	
175 180 185	
GTG GTT GAA GGT ATG CAG TTC GAC CGT GGC TAC CTG TCT CCT TAC TTC	626
Val Val Glu Gly Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe	
190 195 200	

ATC AAC AAG CCG GAA ACT GGC GCA GTA GAA TTG GAA AGC CCG TTC ATC Ile Asn Lys Pro Glu Thr Gly Ala Val Glu Leu Glu Ser Pro Phe Ile 205 210 215 220	674
CTG CTG GCT GAC AAG AAA ATC TCC AAC ATC CGC GAA ATG CTG CCG GTT Leu Leu Ala Asp Lys Lys Ile Ser Asn Ile Arg Glu Met Leu Pro Val 225 230 235	722
CTG GAA GCT GTA GCG AAA GCA GGC AAA CCG CTG CTG ATC ATC GCT GAA Leu Glu Ala Val Ala Lys Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu 240 245 250	770
GAT GTT GAA GGC GAA GCG CTG GCA ACT CTG GTT GTT AAC ACC ATG CGC Asp Val Glu Gly Glu Ala Leu Ala Thr Leu Val Val Asn Thr Met Arg 255 260 265	818
GGT ATC GTA AAA GTC GCT GCG GTT AAA GCA CCT GGC TTC GGC GAT CGT Gly Ile Val Lys Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg 270 275 280	866
CGT AAA GCA ATG CTG CAG GAT ATC GCT ACC CTG ACC GGT GGT ACC GTT Arg Lys Ala Met Leu Gln Asp Ile Ala Thr Leu Thr Gly Gly Thr Val 285 290 295 300	914
ATC TCT GAA GAG ATC GGT ATG GAG CTG GAA AAA GCA ACT CTG GAA GAT Ile Ser Glu Glu Ile Gly Met Glu Leu Glu Lys Ala Thr Leu Glu Asp 305 310 315	962
CTG GGC CAG GCG AAA CGC GTT GTT ATC AAC AAA GAT ACC ACC ACC ACC ATC Leu Gly Gln Ala Lys Arg Val Val Ile Asn Lys Asp Thr Thr Thr Ile 320 325 330	1010
ATC GAT GGC GTG GGC GAC GAA GCT GCA ATC CAG GGT CGC GTG ACT CAG Ile Asp Gly Val Gly Asp Glu Ala Ala Ile Gln Gly Arg Val Thr Gln 335 340 345	1058
ATT CGT CAG CAG ATC GAA GAA GCA ACT TCC GAC TAT GAC CGT GAA AAA Ile Arg Gln Gln Ile Glu Glu Ala Thr Ser Asp Tyr Asp Arg Glu Lys 350 355 360	1106
CTG CAG GAG CGC GTA GCG AAA CTG GCA GGC GGC GTT GCG GTT ATC AAA Leu Gln Glu Arg Val Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys 365 370 375 380	1154
GTT GGT GCT GCG ACT GAA GTT GAA ATG AAA GAG AAG AAA GCC CGC GTT Val Gly Ala Ala Thr Glu Val Glu Met Lys Glu Lys Lys Ala Arg Val 385 390 395	1202
GAA GAT GCC CTG CAC GCT ACC CGT GCT GCG GTA GAA GAA GGC GTG GTT Glu Asp Ala Leu His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val 400 405 410	1250
GCT GGT GGT GGC GTT GCG CTG ATT CGC GTA GCG TCT AAA ATT GCC GGC Ala Gly Gly Val Ala Leu Ile Arg Val Ala Ser Lys Ile Ala Gly 415 420 425	1298

CTG AAA GGT CAG AAC GAA GAC CAG AAC GTA GGT ATC AAA GTT GCG CTG	1346
Leu Lys Gly Gln Asn Glu Asp Gln Asn Val Gly Ile Lys Val Ala Leu	
430 435 440	
CGC GCA ATG GAA TCC CCA CTG CGT CAA ATC GTA CTG AAC TGC GGC GAA	1394
Arg Ala Met Glu Ser Pro Leu Arg Gln Ile Val Leu Asn Cys Gly Glu	
445 450 455 460	
GAG CCG TCT GTA GTG GCT AAC ACC GTG AAA GCC GGT GAC GGT AAC TAC	1442
Glu Pro Ser Val Val Ala Asn Thr Val Lys Ala Gly Asp Gly Asn Tyr	
465 470 475	
GGT TAC AAC GCT GCA ACT GAA GAA TAC GGC AAC ATG ATC GAC ATG GGT	1490
Gly Tyr Asn Ala Ala Thr Glu Glu Tyr Gly Asn Met Ile Asp Met Gly	
480 485 490	
ATC CTG GAT CCA ACC AAA GTA ACT CGT TCT GCT CTG CAG TAC GCG GCT	1538
Ile Leu Asp Pro Thr Lys Val Thr Arg Ser Ala Leu Gln Tyr Ala Ala	
495 500 505	
TCT GTT GCG GGT CTG ATG ATC ACC ACC GAG TGC ATG GTT ACC GAC CTG	1586
Ser Val Ala Gly Leu Met Ile Thr Thr Glu Cys Met Val Thr Asp Leu	
510 515 520	
CCG AAA GGC GAT GCA CCT GAC TTA GGT GCT GCT GGT GGT ATG GGC GGC	1634
Pro Lys Gly Asp Ala Pro Asp Leu Gly Ala Ala Gly Gly Met Gly Gly	
525 530 535 540	
ATG GGC GGA ATG ATG TGATCAAGCC GAATTC	1665
Met Gly Gly Met Met	
545	

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 545 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala Arg Val Lys Met	
1 5 10 15	
Leu Arg Gly Val Asn Val Leu Ala Asp Ala Val Lys Val Thr Leu Gly	
20 25 30	
Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe Gly Ala Pro Thr	
35 40 45	
Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile Glu Leu Glu Asp	

50 55 60

Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Ser Lys
65 70 75 80

Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala
85 90 95

Gln Ser Ile Ile Thr Glu Gly Leu Lys Ala Val Ala Ala Gly Met Asn
100 105 110

Pro Met Asp Leu Lys Arg Gly Ile Asp Lys Ala Val Ala Ala Val
115 120 125

Glu Glu Leu Lys Ala Leu Ser Val Pro Cys Ser Asp Ser Lys Ala Ile
130 135 140

Ala Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Glu Thr Val Gly Lys
145 150 155 160

Leu Ile Ala Glu Ala Met Asp Lys Val Gly Lys Glu Gly Val Ile Thr
165 170 175

Val Glu Asp Gly Thr Gly Leu Gln Asp Glu Leu Asp Val Val Glu Gly
180 185 190

Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Lys Pro
195 200 205

Glu Thr Gly Ala Val Glu Leu Glu Ser Pro Phe Ile Leu Leu Ala Asp
210 215 220

Lys Lys Ile Ser Asn Ile Arg Glu Met Leu Pro Val Leu Glu Ala Val
225 230 235 240

Ala Lys Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly
245 250 255

Glu Ala Leu Ala Thr Leu Val Val Asn Thr Met Arg Gly Ile Val Lys
260 265 270

Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met
275 280 285

Leu Gln Asp Ile Ala Thr Leu Thr Gly Gly Thr Val Ile Ser Glu Glu
290 295 300

Ile Gly Met Glu Leu Glu Lys Ala Thr Leu Glu Asp Leu Gly Gln Ala
305 310 315 320

Lys Arg Val Val Ile Asn Lys Asp Thr Thr Thr Ile Ile Asp Gly Val
325 330 335

Gly Asp Glu Ala Ala Ile Gln Gly Arg Val Thr Gln Ile Arg Gln Gln
340 345 350

Ile Glu Glu Ala Thr Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg
355 360 365

Val Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala
370 375 380

Thr Glu Val Glu Met Lys Glu Lys Lys Ala Arg Val Glu Asp Ala Leu
385 390 395 400

His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val Ala Gly Gly Gly
405 410 415

Val Ala Leu Ile Arg Val Ala Ser Lys Ile Ala Gly Leu Lys Gly Gln
420 425 430

Asn Glu Asp Gln Asn Val Gly Ile Lys Val Ala Leu Arg Ala Met Glu
435 440 445

Ser Pro Leu Arg Gln Ile Val Leu Asn Cys Gly Glu Pro Ser Val
450 455 460

Val Ala Asn Thr Val Lys Ala Gly Asp Gly Asn Tyr Gly Tyr Asn Ala
465 470 475 480

Ala Thr Glu Glu Tyr Gly Asn Met Ile Asp Met Gly Ile Leu Asp Pro
485 490 495

Thr Lys Val Thr Arg Ser Ala Leu Gln Tyr Ala Ala Ser Val Ala Gly
500 505 510

Leu Met Ile Thr Thr Glu Cys Met Val Thr Asp Leu Pro Lys Gly Asp
515 520 525

Ala Pro Asp Leu Gly Ala Ala Gly Gly Met Gly Gly Met Gly Gly Met
530 535 540

Met
545

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1654 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 15..1637

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GAATTCGGCT TCAT ATG GCA AAA GAA ATT AAA TTT TCA TCA GAT GCC CGT	50
Met Ala Lys Glu Ile Lys Phe Ser Ser Asp Ala Arg	
1 5 10	
TCA GCT ATG GTC CGT GGT GTC GAT ATC CTT GCA GAT ACT GTT AAA GTA	98
Ser Ala Met Val Arg Gly Val Asp Ile Leu Ala Asp Thr Val Lys Val	
15 20 25	
ACT TTG GGA CCA AAA GGT CGC AAT GTC GTT CTT GAA AAG TCA TTC GGT	146
Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys Ser Phe Gly	
30 35 40	
TCA CCC TTG ATT ACC AAT GAC GGT GTG ACT ATT GCC AAA GAA ATT GAA	194
Ser Pro Leu Ile Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu	
45 50 55 60	
TTA GAA GAC CAT TTT GAA AAT ATG GGT GCC AAA TTG GTA TCA GAA GTA	242
Leu Glu Asp His Phe Glu Asn Met Gly Ala Lys Leu Val Ser Glu Val	
65 70 75	
GCT TCA AAA ACC AAT GAT ATC GCA GGT GAT GGA ACT ACA ACT GCA ACT	290
Ala Ser Lys Thr Asn Asp Ile Ala Gly Asp Gly Thr Thr Ala Thr	
80 85 90	
GTT TTG ACC CAA GCA ATC GTC CGT GAA GGA ATC AAA AAC GTC ACA GCA	338
Val Leu Thr Gln Ala Ile Val Arg Glu Gly Ile Lys Asn Val Thr Ala	
95 100 105	
GGT GCA AAT CCA ATC GGT ATT CGT CGT GGG ATT GAA ACA GCA GTT GCC	386
Gly Ala Asn Pro Ile Gly Ile Arg Arg Gly Ile Glu Thr Ala Val Ala	
110 115 120	
GCA GCA GTT GAA GCT TTG AAA AAC AAC GTC ATC CCT GTT GCC AAT AAA	434
Ala Ala Val Glu Ala Leu Lys Asn Asn Val Ile Pro Val Ala Asn Lys	
125 130 135 140	
GAA GCT ATC GCT CAA GTT GCA GCC GTA TCT TCT CGT TCT GAA AAA GTT	482
Glu Ala Ile Ala Gln Val Ala Ala Val Ser Ser Arg Ser Glu Lys Val	
145 150 155	
GGT GAG TAC ATC TCT GAA GCA ATG GAA AAA GTT GGC AAA GAC GGT GTC	530
Gly Glu Tyr Ile Ser Glu Ala Met Glu Lys Val Gly Lys Asp Gly Val	
160 165 170	
ATC ACC ATC GAA GAG TCA CGT GGT ATG GAA ACA GAG CTT GAA GTC GTA	578
Ile Thr Ile Glu Glu Ser Arg Gly Met Glu Thr Glu Leu Glu Val Val	
175 180 185	
GAA GGA ATG CAG TTT GAC CGT GGT TAC CTT TCA CAG TAC ATG GTG ACA	626
Glu Gly Met Gln Phe Asp Arg Gly Tyr Leu Ser Gln Tyr Met Val Thr	
190 195 200	
GAT AGC GAA AAA ATG GTG GCT GAC CTT GAA AAT CCG TAC ATT TTG ATT	674

Asp Ser Glu Lys Met Val Ala Asp Leu Glu Asn Pro Tyr Ile Leu Ile			
205	210	215	220
ACA GAC AAG AAA ATT TCC AAT ATC CAA GAA ATC TTG CCA CTT TTG GAA			722
Thr Asp Lys Lys Ile Ser Asn Ile Gln Glu Ile Leu Pro Leu Leu Glu			
225	230	235	
AGC ATT CTC CAA AGC AAT CGT CCA CTC TTG ATT ATT GCG GAT GAT GTG			770
Ser Ile Leu Gln Ser Asn Arg Pro Leu Leu Ile Ile Ala Asp Asp Val			
240	245	250	
GAT GGT GAG GCT CTT CCA ACT CTT GTT TTG AAC AAG ATT CGT GGA ACC			818
Asp Gly Glu Ala Leu Pro Thr Leu Val Leu Asn Lys Ile Arg Gly Thr			
255	260	265	
TTC AAC GTA GTA GCA GTC AAG GCA CCT GGT TTT GGT GAC CGT CGC AAA			866
Phe Asn Val Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys			
270	275	280	
GCC ATG CTT GAA GAT ATC GCC ATC TTA ACA GGC GGA ACA GTT ATC ACA			914
Ala Met Leu Glu Asp Ile Ala Ile Leu Thr Gly Gly Thr Val Ile Thr			
285	290	295	300
GAA GAC CTT GGT CTT GAG TTG AAA GAT GCG ACA ATT GAA GCT CTT GGT			962
Glu Asp Leu Gly Leu Glu Leu Lys Asp Ala Thr Ile Glu Ala Leu Gly			
305	310	315	
CAA GCA GCG AGA GTG ACC GTG GAC AAA GAT AGC ACG GTT ATT GTA GAA			1010
Gln Ala Ala Arg Val Thr Val Asp Lys Asp Ser Thr Val Ile Val Glu			
320	325	330	
GGT GCA GGA AAT CCT GAA GCG ATT TCT CAC CGT GTT GCG GTT ATC AAG			1058
Gly Ala Gly Asn Pro Glu Ala Ile Ser His Arg Val Ala Val Ile Lys			
335	340	345	
TCT CAA ATC GAA ACT ACA ACT TCT GAA TTT GAC CGT GAA AAA TTG CAA			1106
Ser Gln Ile Glu Thr Thr Ser Glu Phe Asp Arg Glu Lys Leu Gln			
350	355	360	
GAA CGC TTG GCC AAA TTG TCA GGT GGT GTA GCG GTT ATT AAG GTC GGA			1154
Glu Arg Leu Ala Lys Leu Ser Gly Gly Val Ala Val Ile Lys Val Gly			
365	370	375	380
GCC GCA ACT GAA ACT GAG TTG AAA GAA ATG AAA CTC CGC ATT GAA GAT			1202
Ala Ala Thr Glu Thr Glu Leu Lys Glu Met Lys Leu Arg Ile Glu Asp			
385	390	395	
GCC CTC AAC GCT ACT CGT GCA GCT GTT GAA GAA GGT ATT GTT GCA GGT			1250
Ala Leu Asn Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly			
400	405	410	
GGT GGA ACA GCT CTT GCC AAT GTG ATT CCA GCT GTT GCT ACC TTG GAA			1298
Gly Gly Thr Ala Leu Ala Asn Val Ile Pro Ala Val Ala Thr Leu Glu			
415	420	425	

TTG ACA GGA GAT GAA GCA ACA GGA CGT AAT ATT GTT CTC CGT GCT TTG	1346
Leu Thr Gly Asp Glu Ala Thr Gly Arg Asn Ile Val Leu Arg Ala Leu	
430 435 440	
GAA GAA CCT GTT CGT CAA ATT GCT CAC AAT GCA GGA TTT GAA GGA TCT	1394
Glu Glu Pro Val Arg Gln Ile Ala His Asn Ala Gly Phe Glu Gly Ser	
445 450 455 460	
ATC GTT ATC GAT CGT TTG AAA AAT GCT GAG CTT GGT ATA GGA TTC AAC	1442
Ile Val Ile Asp Arg Leu Lys Asn Ala Glu Leu Gly Ile Gly Phe Asn	
465 470 475	
GCA GCA ACT GGC GAG TGG GTT AAC ATG ATT GAT CAA GGT ATC ATT GAT	1490
Ala Ala Thr Gly Glu Trp Val Asn Met Ile Asp Gln Gly Ile Ile Asp	
480 485 490	
CCA GTT AAA GTG AGT CGT TCA GCC CTA CAA AAT GCA GCA TCT GTA GCC	1538
Pro Val Lys Val Ser Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala	
495 500 505	
AGC TTG ATT TTG ACA ACA GAA GCA GTC GTA GCC AAT AAA CCA GAA CCA	1586
Ser Leu Ile Leu Thr Thr Glu Ala Val Val Ala Asn Lys Pro Glu Pro	
510 515 520	
GTA GCC CCA GCT CCA GCA ATG GAT CCA AGT ATG ATG GGT GGA ATG GGC	1634
Val Ala Pro Ala Pro Ala Met Asp Pro Ser Met Met Gly Gly Met Gly	
525 530 535 540	
GGA TGATCAAAGC CGAATTG	1654
Gly	

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 541 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Ala Lys Glu Ile Lys Phe Ser Ser Asp Ala Arg Ser Ala Met Val	
1 5 10 15	

Arg Gly Val Asp Ile Leu Ala Asp Thr Val Lys Val Thr Leu Gly Pro	
20 25 30	

Lys Gly Arg Asn Val Val Leu Glu Lys Ser Phe Gly Ser Pro Leu Ile	
35 40 45	

Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp His	
50 55 60	

Phe Glu Asn Met Gly Ala Lys Leu Val Ser Glu Val Ala Ser Lys Thr
65 70 75 80

Asn Asp Ile Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Thr Gln
85 90 95

Ala Ile Val Arg Glu Gly Ile Lys Asn Val Thr Ala Gly Ala Asn Pro
100 105 110

Ile Gly Ile Arg Arg Gly Ile Glu Thr Ala Val Ala Ala Val Glu
115 120 125

Ala Leu Lys Asn Asn Val Ile Pro Val Ala Asn Lys Glu Ala Ile Ala
130 135 140

Gln Val Ala Ala Val Ser Ser Arg Ser Glu Lys Val Gly Glu Tyr Ile
145 150 155 160

Ser Glu Ala Met Glu Lys Val Gly Lys Asp Gly Val Ile Thr Ile Glu
165 170 175

Glu Ser Arg Gly Met Glu Thr Glu Leu Glu Val Val Glu Gly Met Gln
180 185 190

Phe Asp Arg Gly Tyr Leu Ser Gln Tyr Met Val Thr Asp Ser Glu Lys
195 200 205

Met Val Ala Asp Leu Glu Asn Pro Tyr Ile Leu Ile Thr Asp Lys Lys
210 215 220

Ile Ser Asn Ile Gln Glu Ile Leu Pro Leu Leu Glu Ser Ile Leu Gln
225 230 235 240

Ser Asn Arg Pro Leu Leu Ile Ile Ala Asp Asp Val Asp Gly Glu Ala
245 250 255

Leu Pro Thr Leu Val Leu Asn Lys Ile Arg Gly Thr Phe Asn Val Val
260 265 270

Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Glu
275 280 285

Asp Ile Ala Ile Leu Thr Gly Gly Thr Val Ile Thr Glu Asp Leu Gly
290 295 300

Leu Glu Leu Lys Asp Ala Thr Ile Glu Ala Leu Gly Gln Ala Ala Arg
305 310 315 320

Val Thr Val Asp Lys Asp Ser Thr Val Ile Val Glu Gly Ala Gly Asn
325 330 335

Pro Glu Ala Ile Ser His Arg Val Ala Val Ile Lys Ser Gln Ile Glu
340 345 350

Thr Thr Thr Ser Glu Phe Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala
 355 360 365
 Lys Leu Ser Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu
 370 375 380
 Thr Glu Leu Lys Glu Met Lys Leu Arg Ile Glu Asp Ala Leu Asn Ala
 385 390 395 400
 Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Thr Ala
 405 410 415
 Leu Ala Asn Val Ile Pro Ala Val Ala Thr Leu Glu Leu Thr Gly Asp
 420 425 430
 Glu Ala Thr Gly Arg Asn Ile Val Leu Arg Ala Leu Glu Glu Pro Val
 435 440 445
 Arg Gln Ile Ala His Asn Ala Gly Phe Glu Gly Ser Ile Val Ile Asp
 450 455 460
 Arg Leu Lys Asn Ala Glu Leu Gly Ile Gly Phe Asn Ala Ala Thr Gly
 465 470 475 480
 Glu Trp Val Asn Met Ile Asp Gln Gly Ile Ile Asp Pro Val Lys Val
 485 490 495
 Ser Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Leu Ile Leu
 500 505 510
 Thr Thr Glu Ala Val Val Ala Asn Lys Pro Glu Pro Val Ala Pro Ala
 515 520 525
 Pro Ala Met Asp Pro Ser Met Met Gly Gly Met Gly Gly
 530 535 540

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1662 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 15..1646

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GAATTCGGCT TCAT ATG GCG GCT AAA GAT GTA AAA TTC GGT AAC GAC GCT
 Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala

	1	5	10	
CGT GTA AAA ATG CTC CGC GGC GTA AAC GTA CTG GCA GAC GCA GTT AAA				98
Arg Val Lys Met Leu Arg Gly Val Asn Val Leu Ala Asp Ala Val Lys	15	20	25	
GTG ACC CTG GGC CCG AAA GGC CGT AAC GTA GTG CTG GAC AAA TCC TTC				146
Val Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe	30	35	40	
GGC GCG CCA ACC ATC ACG AAA GAT GGT GTT TCT GTA GCA CGT GAA ATC				194
Gly Ala Pro Thr Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile	45	50	55	
45	50	55	60	
GAG CTG GAA GAC AAG TTC GAA AAC ATG GGC GCG CAG ATG GTG AAA GAA				242
Glu Leu Glu Asp Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu	65	70	75	
65	70	75		
GTG GCC TCT AAA GCG AAC GAC GCT GCA GGC GAC GGT ACC ACC ACC GCG				290
Val Ala Ser Lys Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Ala	80	85	90	
80	85	90		
ACC GTG CTG GCT CAG GCT ATC ATC ACC GAA GGT CTG AAA GCC GTT GCT				338
Thr Val Leu Ala Gln Ala Ile Ile Thr Glu Gly Leu Lys Ala Val Ala	95	100	105	
95	100	105		
CGC GGC ATG AAC CCA ATG GAT CTG AAA CGT GGT ATC GAC AAA GCT GTC				386
Ala Gly Met Asn Pro Met Asp Leu Lys Arg Gly Ile Asp Lys Ala Val	110	115	120	
110	115	120		
GCG TCC GCT GTT GAA GAA CTG AAA GCG CTG TCC GTA CCG TGC TCT GAC				434
Ala Ser Ala Val Glu Glu Leu Lys Ala Leu Ser Val Pro Cys Ser Asp	125	130	135	
125	130	135		
125	130	135	140	
TCT AAA GCC ATT GCT CAG GTA GGT ACC ATC TCC GCT AAC TCC GAC GAA				482
Ser Lys Ala Ile Ala Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Glu	145	150	155	
145	150	155		
ACC GTA GGT AAA CTG ATC GCG GAA GCG ATG GAT AAA GTC GGT AAA GAA				530
Thr Val Gly Lys Leu Ile Ala Glu Ala Met Asp Lys Val Gly Lys Glu	160	165	170	
160	165	170		
GGC GTG ATC ACC GTT GAA GAC GGT ACC GGT CTG GAA GAC GAA CTG GAC				578
Gly Val Ile Thr Val Glu Asp Gly Thr Gly Leu Glu Asp Glu Leu Asp	175	180	185	
175	180	185		
GTG GTT GAA GGT ATG CAG TTC GAC CGC GGT TAC CTG TCC CCA TAC TTC				626
Val Val Glu Gly Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe	190	195	200	
190	195	200		
ATC AAC AAG CCA GAA ACT GGC GCT GTT GAG CTG GAA AGC CCG TTC ATC				674
Ile Asn Lys Pro Glu Thr Gly Ala Val Glu Leu Glu Ser Pro Phe Ile	205	210	215	
205	210	215		
205	210	215	220	
CTG CTG GCT GAC AAG AAA ATC TCC AAC ATC CGC GAA ATG CTG CCA GTG				722
CTG CTG GCT GAC AAG AAA ATC TCC AAC ATC CGC GAA ATG CTG CCA GTG				

Leu	Leu	Ala	Asp	Lys	Lys	Ile	Ser	Asn	Ile	Arg	Glu	Met	Leu	Pro	Val	
225									230				235			
CTG	GAA	GCC	GTT	GCG	AAA	GCA	GGC	AAA	CCG	CTG	GTT	ATC	ATT	GCT	GAA	770
Leu	Glu	Ala	Val	Ala	Lys	Ala	Gly	Lys	Pro	Leu	Val	Ile	Ile	Ala	Glu	
240									245				250			
GAC	GTT	GAA	GGC	GAA	GCG	CTG	GCG	ACC	CTG	GTG	GTT	AAC	ACC	ATG	CGT	818
Asp	Val	Glu	Gly	Glu	Ala	Leu	Ala	Thr	Leu	Val	Val	Asn	Thr	Met	Arg	
255								260				265				
GGC	ATC	GTG	AAA	GTG	GCT	GCG	GTT	AAA	GCA	CCT	GGC	TTC	GGC	GAC	CGC	866
Gly	Ile	Val	Lys	Val	Ala	Ala	Val	Lys	Ala	Pro	Gly	Phe	Gly	Asp	Arg	
270								275				280				
CGT	AAA	GCG	ATG	CTG	CAG	GAT	ATC	GCT	ACC	CTG	ACC	GGC	GGT	ACC	GTC	914
Arg	Lys	Ala	Met	Leu	Gln	Asp	Ile	Ala	Thr	Leu	Thr	Gly	Gly	Thr	Val	
285				290					295				300			
ATC	TCT	GAA	GAG	ATC	GGT	ATG	GAG	CTG	GAA	AAA	GCG	ACC	CTG	GAA	GAC	962
Ile	Ser	Glu	Glu	Ile	Gly	Met	Glu	Leu	Glu	Lys	Ala	Thr	Leu	Glu	Asp	
305								310					315			
CTG	GGC	CAG	GCT	AAA	CGT	GTT	GTG	ATC	AAC	AAA	GAC	ACC	ACC	ACC	ATC	1010
Leu	Gly	Gln	Ala	Lys	Arg	Val	Val	Ile	Asn	Lys	Asp	Thr	Thr	Thr	Ile	
320								325					330			
ATC	GAT	GGC	GTG	GGC	GAC	GAA	GCG	GCG	ATT	CAG	GGC	CGT	GTT	GGT	CAG	1058
Ile	Asp	Gly	Val	Gly	Asp	Glu	Ala	Ala	Ile	Gln	Gly	Arg	Val	Gly	Gln	
335								340					345			
ATC	CGT	AAG	CAG	ATC	GAA	GAA	GCC	ACT	TCC	GAT	TAC	GAC	CGT	GAA	AAA	1106
Ile	Arg	Lys	Gln	Ile	Glu	Glu	Ala	Thr	Ser	Asp	Tyr	Asp	Arg	Glu	Lys	
350								355					360			
CTG	CAG	GAG	CGC	GTA	GCG	AAA	CTG	GCA	GGC	GGT	GTT	GCG	GTA	ATC	AAA	1154
Leu	Gln	Glu	Arg	Val	Ala	Lys	Leu	Ala	Gly	Gly	Val	Ala	Val	Ile	Lys	
365								370					375		380	
GTC	GGT	GCT	GCG	ACT	GAA	GTT	GAA	ATG	AAA	GAG	AAA	AAA	GCA	CGC	GTT	1202
Val	Gly	Ala	Ala	Thr	Glu	Val	Glu	Met	Lys	Glu	Lys	Lys	Ala	Arg	Val	
385									390					395		
GAC	GAT	GCC	CTG	CAC	GCG	ACC	CGT	GCT	GCG	GTA	GAA	GAA	GGC	GTG	GTT	1250
Asp	Asp	Ala	Leu	His	Ala	Thr	Arg	Ala	Ala	Val	Glu	Glu	Gly	Val	Val	
400								405					410			
GCT	GGT	GGT	GGT	GTG	GCG	CTG	GTG	CGT	GTT	GCC	GCG	AAA	CTG	TCC	GGC	1298
Ala	Gly	Gly	Gly	Val	Ala	Leu	Val	Arg	Val	Ala	Ala	Lys	Leu	Ser	Gly	
415								420					425			
CTG	ACT	GCT	CAG	AAC	GAA	GAT	CAG	AAC	GTG	GGT	ATC	AAA	GTT	GCG	CTG	1346
Leu	Thr	Ala	Gln	Asn	Glu	Asp	Gln	Asn	Val	Gly	Ile	Lys	Val	Ala	Leu	
430								435					440			

CGC GCA ATG GAA GCT CCA CTG CGT CAG ATC GTG TCC AAC GCC GGT GAA	1394
Arg Ala Met Glu Ala Pro Leu Arg Gln Ile Val Ser Asn Ala Gly Glu	
445 450 455 460	
GAG CCA TCT GTT GTG ACC AAC GTG AAA GCA GGC GAA GGT AAC TAC	1442
Glu Pro Ser Val Val Thr Asn Asn Val Lys Ala Gly Glu Gly Asn Tyr	
465 470 475	
GGT TAC AAC GCA GCA ACT GAA GAA TAC GGC AAC ATG ATC GAC TTC GGT	1490
Gly Tyr Asn Ala Ala Thr Glu Glu Tyr Gly Asn Met Ile Asp Phe Gly	
480 485 490	
ATC CTG GAT CCA ACC AAA GTG ACC CGT TCT GCT CTG CAG TAC GCG GCA	1538
Ile Leu Asp Pro Thr Lys Val Thr Arg Ser Ala Leu Gln Tyr Ala Ala	
495 500 505	
TCT GTC GCT GGC CTG ATG ATC ACC ACC GAG TGC ATG GTG ACC GAC CTG	1586
Ser Val Ala Gly Leu Met Ile Thr Thr Glu Cys Met Val Thr Asp Leu	
510 515 520	
CCT AAA GGC GAC GCA CCT GAC TTA GGT GCT GCA GGC ATG GGT GGG ATG	1634
Pro Lys Gly Asp Ala Pro Asp Leu Gly Ala Ala Gly Met Gly Gly Met	
525 530 535 540	
GGC GGT ATG ATG TGATCAAGCC GAATTC	1662
Gly Gly Met Met	

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 544 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala Arg Val Lys Met	
1 5 10 15	
Leu Arg Gly Val Asn Val Leu Ala Asp Ala Val Lys Val Thr Leu Gly	
20 25 30	
Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe Gly Ala Pro Thr	
35 40 45	
Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile Glu Leu Glu Asp	
50 55 60	
Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Ser Lys	
65 70 75 80	

Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala
85 90 95

Gln Ala Ile Ile Thr Glu Gly Leu Lys Ala Val Ala Ala Gly Met Asn
100 105 110

Pro Met Asp Leu Lys Arg Gly Ile Asp Lys Ala Val Ala Ser Ala Val
115 120 125

Glu Glu Leu Lys Ala Leu Ser Val Pro Cys Ser Asp Ser Lys Ala Ile
130 135 140

Ala Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Glu Thr Val Gly Lys
145 150 155 160

Leu Ile Ala Glu Ala Met Asp Lys Val Gly Lys Glu Gly Val Ile Thr
165 170 175

Val Glu Asp Gly Thr Gly Leu Glu Asp Glu Leu Asp Val Val Glu Gly
180 185 190

Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Lys Pro
195 200 205

Glu Thr Gly Ala Val Glu Leu Glu Ser Pro Phe Ile Leu Leu Ala Asp
210 215 220

Lys Lys Ile Ser Asn Ile Arg Glu Met Leu Pro Val Leu Glu Ala Val
225 230 235 240

Ala Lys Ala Gly Lys Pro Leu Val Ile Ile Ala Glu Asp Val Glu Gly
245 250 255

Glu Ala Leu Ala Thr Leu Val Val Asn Thr Met Arg Gly Ile Val Lys
260 265 270

Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met
275 280 285

Leu Gln Asp Ile Ala Thr Leu Thr Gly Gly Thr Val Ile Ser Glu Glu
290 295 300

Ile Gly Met Glu Leu Glu Lys Ala Thr Leu Glu Asp Leu Gly Gln Ala
305 310 315 320

Lys Arg Val Val Ile Asn Lys Asp Thr Thr Thr Ile Ile Asp Gly Val
325 330 335

Gly Asp Glu Ala Ala Ile Gln Gly Arg Val Gly Gln Ile Arg Lys Gln
340 345 350

Ile Glu Glu Ala Thr Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg
355 360 365

Val Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala

370	375	380
Thr Glu Val Glu Met Lys Glu Lys Lys Ala Arg Val Asp Asp Ala Leu		
385	390	395
His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val Ala Gly Gly Gly		
405	410	415
Val Ala Leu Val Arg Val Ala Ala Lys Leu Ser Gly Leu Thr Ala Gln		
420	425	430
Asn Glu Asp Gln Asn Val Gly Ile Lys Val Ala Leu Arg Ala Met Glu		
435	440	445
Ala Pro Leu Arg Gln Ile Val Ser Asn Ala Gly Glu Glu Pro Ser Val		
450	455	460
Val Thr Asn Asn Val Lys Ala Gly Glu Gly Asn Tyr Gly Tyr Asn Ala		
465	470	475
Ala Thr Glu Glu Tyr Gly Asn Met Ile Asp Phe Gly Ile Leu Asp Pro		
485	490	495
Thr Lys Val Thr Arg Ser Ala Leu Gln Tyr Ala Ala Ser Val Ala Gly		
500	505	510
Leu Met Ile Thr Thr Glu Cys Met Val Thr Asp Leu Pro Lys Gly Asp		
515	520	525
Ala Pro Asp Leu Gly Ala Ala Gly Met Gly Gly Met Gly Gly Met Met		
530	535	540

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1661 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 15..1649

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAATTCCGGCT TCAT ATG GCA AAA GAA ATC AAA TTT TCA GCA GAT GCG CGT	50	
Met Ala Lys Glu Ile Lys Phe Ser Ala Asp Ala Arg		
1	5	10
GCT GCC ATG GTG CGC GGA GTT GAT ATG TTA GCA GAT ACC GTC AAA GTA	98	
Ala Ala Met Val Arg Gly Val Asp Met Leu Ala Asp Thr Val Lys Val		

15	20	25	
ACG CTT GGT CCT AAA GGG CGC AAT GTT GTT CTT GAA AAA GCT TTT GGT			146
Thr Leu Gly Pro Lys Gly Arg Asn Val Val Leu Glu Lys Ala Phe Gly			
30	35	40	
TCT CCC TTA ATT ACT AAT GAC GGG GTA ACC ATT GCT AAA GAG ATC GAA			194
Ser Pro Leu Ile Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu			
45	50	55	60
TTA GAA GAT CAT TTT GAA AAC ATG GGA GCA AAA TTG GTG TCT GAA GTG			242
Leu Glu Asp His Phe Glu Asn Met Gly Ala Lys Leu Val Ser Glu Val			
65	70	75	
GCT TCT AAA ACC AAT GAT ATT GCT GGT GAT GGG ACG ACT ACT GCA ACA			290
Ala Ser Lys Thr Asn Asp Ile Ala Gly Asp Gly Thr Thr Ala Thr			
80	85	90	
GTT TTG ACA CAA GCC ATT GTT CAT GAA GGA CTA AAA AAT GTG ACA GCA			338
Val Leu Thr Gln Ala Ile Val His Glu Gly Leu Lys Asn Val Thr Ala			
95	100	105	
GGT GCT AAT CCA ATT GGT ATC CGT CGA GGC ATT GAA ACA GCA ACA GCA			386
Gly Ala Asn Pro Ile Gly Ile Arg Arg Gly Ile Glu Thr Ala Thr Ala			
110	115	120	
ACA GCT GTT GAA GCC TTG AAA GCC ATT GCT CAA CCT GTA TCT GGC AAG			434
Thr Ala Val Glu Ala Leu Lys Ala Ile Ala Gln Pro Val Ser Gly Lys			
125	130	135	140
GAA GCT ATT GCT CAG GTC GCT GCA GTA TCA TCA CGC TCT GAA AAA GTT			482
Glu Ala Ile Ala Gln Val Ala Ala Val Ser Ser Arg Ser Glu Lys Val			
145	150	155	
GGA GAG TAT ATC TCA GAA GCT ATG GAG CGT GTG GGC AAC GAT GGT GTG			530
Gly Glu Tyr Ile Ser Glu Ala Met Glu Arg Val Gly Asn Asp Gly Val			
160	165	170	
ATT ACC ATC GAA GAA TCT CGA GGT ATG GAA ACA GAA CTT GAA GTG GTT			578
Ile Thr Ile Glu Glu Ser Arg Gly Met Glu Thr Glu Leu Glu Val Val			
175	180	185	
GAA GGC ATG CAA TTT GAC CGT GGT TAC CTG TCT CAA TAC ATG GTC ACA			626
Glu Gly Met Gln Phe Asp Arg Gly Tyr Leu Ser Gln Tyr Met Val Thr			
190	195	200	
GAC AAT GAA AAA ATG GTT GCA GAC CTT GAA AAC CCA TTT ATC TTA ATC			674
Asp Asn Glu Lys Met Val Ala Asp Leu Glu Asn Pro Phe Ile Leu Ile			
205	210	215	220
ACG GAT AAA AAA GTG TCA AAC ATC CAA GAC ATT TTG CCA CTA CTT GAG			722
Thr Asp Lys Lys Val Ser Asn Ile Gln Asp Ile Leu Pro Leu Leu Glu			
225	230	235	
GAA GTT CTT AAA ACC AAC CGT CCA TTA CTC ATT ATT GCA GAT GAT GTG			770

Glu Val Leu Lys Thr Asn Arg Pro Leu Leu Ile Ile Ala Asp Asp Val				
240	245	250		
GAT GGT GAA GCA CTT CCA ACC CTT GTC TTG AAC AAG ATT CGT GGT ACT				818
Asp Gly Glu Ala Leu Pro Thr Leu Val Leu Asn Lys Ile Arg Gly Thr				
255	260	265		
TTC AAT GTG GTT GCT GTC AAA GCG CCA GGA TTT GGT GAT CGT CGT AAA				866
Phe Asn Val Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys				
270	275	280		
GCT ATG CTT GAA GAC ATT GCT ATC TTG ACA GGT GGT ACA GTG ATT ACA				914
Ala Met Leu Glu Asp Ile Ala Ile Leu Thr Gly Gly Thr Val Ile Thr				
285	290	295	300	
GAG GAT CTA GGA CTT GAA TTA AAA GAT GCT ACA ATG ACA GCC CTT GGA				962
Glu Asp Leu Gly Leu Glu Leu Lys Asp Ala Thr Met Thr Ala Leu Gly				
305	310	315		
CAG GCT GCT AAG ATT ACA GTT GAT AAA GAT AGC ACA GTA ATT GTT GAA				1010
Gln Ala Ala Lys Ile Thr Val Asp Lys Asp Ser Thr Val Ile Val Glu				
320	325	330		
GGT TCA GGA AGT TCA GAA GCT ATT GCT AAC CGT ATT GCA CTG ATT AAA				1058
Gly Ser Gly Ser Ser Glu Ala Ile Ala Asn Arg Ile Ala Leu Ile Lys				
335	340	345		
TCG CAA TTA GAA ACA ACA ACT TCT GAC TTT GAC CGT GAA AAA CTA CAA				1106
Ser Gln Leu Glu Thr Thr Ser Asp Phe Asp Arg Glu Lys Leu Gln				
350	355	360		
GAA CGT TTG GCG AAA TTA GCT GGT GTA GCT GTT ATC AAA GTA GGA				1154
Glu Arg Leu Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly				
365	370	375	380	
GCT CCA ACA GAG ACA GCT TTA AAA GAA ATG AAA CTT CGC ATT GAG GAT				1202
Ala Pro Thr Glu Thr Ala Leu Lys Glu Met Lys Leu Arg Ile Glu Asp				
385	390	395		
GCT CTA AAT GCT ACA CGT GCA GCC GTT GAA GAA GGT ATC GTT GCT GGT				1250
Ala Leu Asn Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly				
400	405	410		
GGT GGA ACA GCA CTT ATT ACG GTT ATT GAA AAA GTA GCA GCT CTT GAG				1298
Gly Gly Thr Ala Leu Ile Thr Val Ile Glu Lys Val Ala Ala Leu Glu				
415	420	425		
CTT GAG GGC GAT GAT GCT ACT GGA CGT AAC ATT GTG CTT CGT GCT CTA				1346
Leu Glu Gly Asp Asp Ala Thr Gly Arg Asn Ile Val Leu Arg Ala Leu				
430	435	440		
GAA GAG CCT GTA CGT CAA ATT GCT TTA AAT GCT GGG TAC GAA GGC TCC				1394
Glu Glu Pro Val Arg Gln Ile Ala Leu Asn Ala Gly Tyr Glu Gly Ser				
445	450	455	460	

GTA GTT ATT GAC AAG TTG AAA AAC AGC CCT GCA GGA ACA GGA TTT AAT	1442
Val Val Ile Asp Lys Leu Lys Asn Ser Pro Ala Gly Thr Gly Phe Asn	
465 470 475	
GCT GCA ACA GGT GAG TGG GTT GAT ATG ATT AAA ACA GGA ATC ATT GAC	1490
Ala Ala Thr Gly Glu Trp Val Asp Met Ile Lys Thr Gly Ile Ile Asp	
480 485 490	
CCT GTC AAA GTA ACA CGA TCA GCG CTT CAA AAT GCA GCT TCT GTA GCT	1538
Pro Val Lys Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala	
495 500 505	
AGT CTT ATT TTG ACA ACA GAA GCA GTT GTT GCT AAT AAA CCT GAA CCA	1586
Ser Leu Ile Leu Thr Thr Glu Ala Val Val Ala Asn Lys Pro Glu Pro	
510 515 520	
GCT ACG CCA GCG CCA GCA ATG CCA GCA GGT ATG GAT CCA GGA ATG ATG	1634
Ala Thr Pro Ala Pro Ala Met Pro Ala Gly Met Asp Pro Gly Met Met	
525 530 535 540	
GGT GGG ATG GGC GGA TAAGCCGAAT TC	1661
Gly Gly Met Gly Gly	
545	

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 545 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ala Lys Glu Ile Lys Phe Ser Ala Asp Ala Arg Ala Ala Met Val	
1 5 10 15	

Arg Gly Val Asp Met Leu Ala Asp Thr Val Lys Val Thr Leu Gly Pro	
20 25 30	

Lys Gly Arg Asn Val Val Leu Glu Lys Ala Phe Gly Ser Pro Leu Ile	
35 40 45	

Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp His	
50 55 60	

Phe Glu Asn Met Gly Ala Lys Leu Val Ser Glu Val Ala Ser Lys Thr	
65 70 75 80	

Asn Asp Ile Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Thr Gln	
85 90 95	

Ala Ile Val His Glu Gly Leu Lys Asn Val Thr Ala Gly Ala Asn Pro	
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100	105	110
Ile Gly Ile Arg Arg Gly Ile Glu Thr Ala Thr Ala Thr Ala Val Glu		
115	120	125
Ala Leu Lys Ala Ile Ala Gln Pro Val Ser Gly Lys Glu Ala Ile Ala		
130	135	140
Gln Val Ala Ala Val Ser Ser Arg Ser Glu Lys Val Gly Glu Tyr Ile		
145	150	155
Ser Glu Ala Met Glu Arg Val Gly Asn Asp Gly Val Ile Thr Ile Glu		
165	170	175
Glu Ser Arg Gly Met Glu Thr Glu Leu Glu Val Val Glu Gly Met Gln		
180	185	190
Phe Asp Arg Gly Tyr Leu Ser Gln Tyr Met Val Thr Asp Asn Glu Lys		
195	200	205
Met Val Ala Asp Leu Glu Asn Pro Phe Ile Leu Ile Thr Asp Lys Lys		
210	215	220
Val Ser Asn Ile Gln Asp Ile Leu Pro Leu Leu Glu Glu Val Leu Lys		
225	230	235
240		
Thr Asn Arg Pro Leu Leu Ile Ile Ala Asp Asp Val Asp Gly Glu Ala		
245	250	255
Leu Pro Thr Leu Val Leu Asn Lys Ile Arg Gly Thr Phe Asn Val Val		
260	265	270
Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Glu		
275	280	285
Asp Ile Ala Ile Leu Thr Gly Gly Thr Val Ile Thr Glu Asp Leu Gly		
290	295	300
Leu Glu Leu Lys Asp Ala Thr Met Thr Ala Leu Gly Gln Ala Ala Lys		
305	310	315
320		
Ile Thr Val Asp Lys Asp Ser Thr Val Ile Val Glu Gly Ser Gly Ser		
325	330	335
Ser Glu Ala Ile Ala Asn Arg Ile Ala Leu Ile Lys Ser Gln Leu Glu		
340	345	350
Thr Thr Thr Ser Asp Phe Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala		
355	360	365
Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Pro Thr Glu		
370	375	380
Thr Ala Leu Lys Glu Met Lys Leu Arg Ile Glu Asp Ala Leu Asn Ala		
385	390	395
400		

Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Gly Thr Ala
 405 410 415

Leu Ile Thr Val Ile Glu Lys Val Ala Ala Leu Glu Leu Glu Gly Asp
 420 425 430

Asp Ala Thr Gly Arg Asn Ile Val Leu Arg Ala Leu Glu Glu Pro Val
 435 440 445

Arg Gln Ile Ala Leu Asn Ala Gly Tyr Glu Gly Ser Val Val Ile Asp
 450 455 460

Lys Leu Lys Asn Ser Pro Ala Gly Thr Gly Phe Asn Ala Ala Thr Gly
 465 470 475 480

Glu Trp Val Asp Met Ile Lys Thr Gly Ile Ile Asp Pro Val Lys Val
 485 490 495

Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Leu Ile Leu
 500 505 510

Thr Thr Glu Ala Val Val Ala Asn Lys Pro Glu Pro Ala Thr Pro Ala
 515 520 525

Pro Ala Met Pro Ala Gly Met Asp Pro Gly Met Met Gly Gly Met Gly
 530 535 540

Gly
 545

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 544 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Ala Lys Glu Ile Lys Phe Ser Glu Glu Ala Arg Arg Ala Met Leu
 1 5 10 15

Arg Gly Val Asp Ala Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
 20 25 30

Lys Gly Arg Asn Val Val Leu Glu Lys Lys Phe Gly Ser Pro Leu Ile
 35 40 45

Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp Ala

50	55	60
Phe Glu Asn Met Gly Ala Lys Leu Val Ala Glu Val Ala Ser Lys Thr		
65	70	75
Asn Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln		
85	90	95
Ala Met Ile Arg Glu Gly Leu Lys Asn Val Thr Ala Gly Ala Asn Pro		
100	105	110
Val Gly Val Arg Lys Gly Met Glu Gln Ala Val Ala Val Ala Ile Glu		
115	120	125
Asn Leu Lys Glu Ile Ser Lys Pro Ile Glu Gly Lys Glu Ser Ile Ala		
130	135	140
Gln Val Ala Ala Ile Ser Ala Ala Asp Glu Glu Val Gly Ser Leu Ile		
145	150	155
Ala Glu Ala Met Glu Arg Val Gly Asn Asp Gly Val Ile Thr Ile Glu		
165	170	175
Glu Ser Lys Gly Phe Thr Thr Glu Leu Glu Val Val Glu Gly Met Gln		
180	185	190
Phe Asp Arg Gly Tyr Ala Ser Pro Tyr Met Val Thr Asp Ser Asp Lys		
195	200	205
Met Glu Ala Val Leu Asp Asn Pro Tyr Ile Leu Ile Thr Asp Lys Lys		
210	215	220
Ile Thr Asn Ile Gln Glu Ile Leu Pro Val Leu Glu Gln Val Val Gln		
225	230	235
Gln Gly Lys Pro Leu Leu Leu Ile Ala Glu Asp Val Glu Gly Glu Ala		
245	250	255
Leu Ala Thr Leu Val Val Asn Lys Leu Arg Gly Thr Phe Asn Ala Val		
260	265	270
Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Glu		
275	280	285
Asp Ile Ala Val Leu Thr Gly Gly Glu Val Ile Thr Glu Asp Leu Gly		
290	295	300
Leu Asp Leu Lys Ser Thr Gln Ile Ala Gln Leu Gly Arg Ala Ser Lys		
305	310	315
Val Val Val Thr Lys Glu Asn Thr Thr Ile Val Glu Gly Ala Gly Glu		
325	330	335
Thr Asp Lys Ile Ser Ala Arg Val Thr Gln Ile Arg Ala Gln Val Glu		
340	345	350

Glu Thr Thr Ser Glu Phe Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala
 355 360 365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu
 370 375 380

Thr Glu Leu Lys Glu Arg Lys Leu Arg Ile Glu Asp Ala Leu Asn Ser
 385 390 395 400

Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ser Gly Gly Thr Ala
 405 410 415

Leu Val Asn Val Tyr Asn Lys Val Ala Ala Val Glu Ala Glu Gly Asp
 420 425 430

Ala Gln Thr Gly Ile Asn Ile Val Leu Arg Ala Leu Glu Glu Pro Ile
 435 440 445

Arg Gln Ile Ala His Asn Ala Gly Leu Glu Gly Ser Val Ile Val Glu
 450 455 460

Arg Leu Lys Asn Glu Glu Ile Gly Val Gly Phe Asn Ala Ala Thr Gly
 465 470 475 480

Glu Trp Val Asn Met Ile Glu Lys Gly Ile Val Asp Pro Thr Lys Val
 485 490 495

Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ala Met Phe Leu
 500 505 510

Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Glu Asn Gly Gly Gly
 515 520 525

Ala Gly Met Pro Asp Met Gly Gly Met Gly Gly Met Gly Gly Met Met
 530 535 540

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 539 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Ala Lys Thr Leu Leu Phe Gly Glu Ala Arg Arg Ser Met Gln
 1 5 10 15

Ala Gly Val Asp Lys Leu Ala Asn Thr Val Lys Val Thr Leu Gly Pro
20 25 30

Lys Gly Arg Asn Val Ile Leu Asp Lys Lys Phe Gly Ser Pro Leu Ile
35 40 45

Thr Asn Asp Gly Val Thr Ile Ala Arg Glu Ile Glu Leu Glu Asp Ala
50 55 60

Tyr Glu Asn Met Gly Ala Gln Leu Val Lys Glu Val Ala Thr Lys Thr
65 70 75 80

Asn Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Leu Leu Ala Gln
85 90 95

Ala Ile Ile Arg Glu Gly Leu Lys Asn Val Thr Ala Gly Ala Asn Pro
100 105 110

Ile Leu Ile Arg Asn Gly Ile Lys Thr Ala Val Glu Lys Ala Val Glu
115 120 125

Glu Ile Gln Lys Ile Ser Lys Pro Val Asn Gly Lys Glu Asp Ile Ala
130 135 140

Arg Val Ala Ala Ile Ser Ala Ala Asp Glu Lys Ile Gly Lys Leu Ile
145 150 155 160

Ala Asp Ala Met Glu Lys Val Gly Asn Glu Gly Val Ile Thr Val Glu
165 170 175

Glu Ser Lys Ser Met Gly Thr Glu Leu Asp Val Val Glu Gly Met Gln
180 185 190

Phe Asp Arg Gly Tyr Val Ser Ala Tyr Met Val Thr Asp Thr Glu Lys
195 200 205

Met Glu Ala Val Leu Asp Asn Pro Leu Val Leu Ile Thr Asp Lys Lys
210 215 220

Ile Ser Asn Ile Gln Asp Leu Leu Pro Leu Leu Glu Gln Ile Val Gln
225 230 235 240

Ala Gly Lys Lys Leu Leu Ile Ile Ala Asp Asp Ile Glu Gly Glu Ala
245 250 255

Met Thr Thr Leu Val Val Asn Lys Leu Arg Gly Thr Phe Thr Cys Val
260 265 270

Gly Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Glu Met Leu Gln
275 280 285

Asp Ile Ala Thr Leu Thr Gly Gly Val Val Ile Ser Asp Glu Val Gly
290 295 300

Gly Asp Leu Lys Glu Ala Thr Leu Asp Met Leu Gly Glu Ala Glu Ser

305	310	315	320
Val Lys Val Thr Lys Glu Ser Thr Thr Ile Val Asn Gly Arg Gly Asn			
325		330	335
Ser Glu Glu Ile Lys Asn Arg Ile Asn Gln Ile Lys Leu Gln Leu Glu			
340		345	350
Ala Thr Thr Ser Glu Phe Asp Lys Glu Lys Leu Gln Glu Arg Leu Ala			
355		360	365
Lys Leu Ala Gly Gly Val Ala Val Val Lys Val Gly Ala Ala Thr Glu			
370		375	380
Thr Glu Leu Lys Glu Ser Lys Leu Arg Ile Glu Asp Ala Leu Ala Ala			
385		390	395
Thr Lys Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Thr Ala			
405		410	415
Tyr Val Asn Val Ile Asn Glu Val Ala Lys Leu Thr Ser Asp Ile Gln			
420		425	430
Asp Glu Gln Val Gly Ile Asn Ile Ile Val Arg Ser Leu Glu Glu Pro			
435		440	445
Met Arg Gln Ile Ala His Asn Ala Gly Leu Glu Gly Ser Val Ile Ile			
450		455	460
Glu Lys Val Lys Asn Ser Asp Ala Gly Val Gly Phe Asp Ala Leu Arg			
465		470	480
Gly Glu Tyr Lys Asp Met Ile Lys Ala Gly Ile Val Asp Pro Thr Lys			
485		490	495
Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Thr Phe			
500		505	510
Leu Thr Thr Glu Ala Ala Val Ala Asp Ile Pro Glu Lys Glu Met Pro			
515		520	525
Gln Gly Ala Gly Met Gly Met Asp Gly Met Tyr			
530		535	

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 551 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Ala Asn Met Val Val Thr Gly Glu Gln Leu Asp Lys Ser Ile Arg
1 5 10 15

Glu Val Val Arg Ile Leu Glu Asp Ala Val Gly Cys Thr Ala Gly Pro
20 25 30

Lys Gly Leu Thr Val Ala Ile Ser Lys Pro Tyr Gly Ala Pro Glu Val
35 40 45

Thr Lys Asp Gly Tyr Lys Val Met Lys Ser Ile Lys Pro Glu Asp Pro
50 55 60

Leu Ala Leu Ala Ile Ala Asn Ile Ile Ala Gln Ser Ala Ser Gln Cys
65 70 75 80

Asn Asp Lys Val Gly Asp Gly Thr Thr Cys Ser Ile Leu Thr Ala
85 90 95

Lys Val Ile Glu Glu Val Ser Lys Val Lys Ala Ala Gly Ala Asp Ile
100 105 110

Ile Cys Val Arg Glu Gly Val Leu Lys Ala Lys Glu Ala Val Leu Glu
115 120 125

Ala Leu Lys Cys Met Lys Arg Glu Val Leu Ser Glu Glu Glu Ile Ala
130 135 140

Gln Val Ala Thr Ile Ser Ala Asn Gly Asp Lys Asn Ile Gly Thr Lys
145 150 155 160

Ile Ala Gln Cys Val Lys Glu Val Gly Lys Asp Gly Val Ile Thr Val
165 170 175

Glu Glu Ser Lys Gly Phe Lys Glu Leu Asp Val Glu Lys Thr Asp Gly
180 185 190

Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Val Thr Asn Ser
195 200 205

Glu Lys Met Leu Val Glu Phe Glu Asn Pro Tyr Ile Leu Leu Thr Glu
210 215 220

Lys Lys Leu Asn Ile Ile Gln Pro Leu Leu Pro Ile Leu Glu Asn Ile
225 230 235 240

Ala Arg Ser Gly Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly
245 250 255

Glu Ala Leu Ser Thr Leu Val Leu Asn Lys Leu Arg Gly Gly Leu His
260 265 270

Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Asp Met

275	280	285
Leu Gly Asp Ile Ala Ile Leu Thr Gly Ala Lys His Val Ile Asn Asp		
290	295	300
Glu Leu Ala Ile Lys Met Glu Asp Leu Thr Leu Cys Asp Leu Gly Thr		
305	310	315
320		
Ala Lys Asn Ile Arg Ile Thr Lys Asp Thr Thr Thr Ile Ile Gly Ser		
325	330	335
Val Asp Asn Ser Cys Ala His Val Gln Ser Arg Ile Cys Gln Ile Arg		
340	345	350
Met Gln Ile Asp Asn Ser Thr Ser Asp Tyr Asp Lys Glu Lys Leu Gln		
355	360	365
Glu Arg Leu Ala Lys Leu Ser Gly Gly Val Ala Val Leu Lys Val Gly		
370	375	380
Gly Ser Ser Glu Val Glu Val Lys Glu Arg Lys Asp Arg Val Glu Asp		
385	390	395
400		
Ala Leu His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val Pro Gly		
405	410	415
Gly Gly Ala Ala Leu Leu Tyr Thr Leu Ser Ala Leu Asp Asn Leu Lys		
420	425	430
Ser Lys Asn Asp Asp Glu Gln Leu Gly Ile Asn Ile Val Lys Arg Ala		
435	440	445
Leu Gln Ala Pro Ile Lys Arg Ile Ile Lys Asn Ala Gly Ser Glu Asn		
450	455	460
Ala Pro Cys Val Ile Ala His Leu Leu Lys Gln Asn Asp Lys Glu Leu		
465	470	475
480		
Ile Phe Asn Val Asp Val Thr Asn Phe Ala Asn Ala Phe Thr Ser Gly		
485	490	495
Val Ile Asp Pro Leu Lys Val Val Arg Ile Ala Phe Asp Phe Ala Val		
500	505	510
Ser Leu Ala Ala Val Phe Met Thr Leu Asn Ala Ile Val Val Asp Ile		
515	520	525
Pro Ser Lys Asp Asp Asn Ser Ala Ala Gly Gly Ala Gly Met Gly Gly		
530	535	540
Met Gly Gly Met Gly Gly Phe		
545	550	

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 548 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Ala Ala Lys Asp Val Lys Phe Gly Asn Asp Ala Arg Val Lys Met
1 5 10 15

Leu Asn Gly Val Asn Ile Leu Ala Asp Ala Val Lys Val Thr Leu Gly
20 25 30

Pro Lys Gly Arg Asn Val Val Leu Asp Lys Ser Phe Gly Ala Pro Thr
35 40 45

Ile Thr Lys Asp Gly Val Ser Val Ala Arg Glu Ile Glu Leu Glu Asp
50 55 60

Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Ser Lys
65 70 75 80

Ala Asn Asp Ala Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala
85 90 95

Gln Ala Ile Val Asn Glu Gly Leu Lys Ala Val Ala Ala Gly Met Asn
100 105 110

Pro Met Asp Leu Lys Arg Gly Ile Asp Lys Ala Val Asn Ser Val Val
115 120 125

Ala Glu Leu Lys Asn Leu Ser Lys Pro Cys Glu Thr Ser Lys Glu Ile
130 135 140

Glu Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Ser Ile Val Gly Gln
145 150 155 160

Leu Ile Ala Gln Ala Met Glu Lys Val Gly Lys Glu Gly Val Ile Thr
165 170 175

Val Glu Asp Gly Thr Gly Leu Glu Asp Glu Leu Asp Val Val Glu Gly
180 185 190

Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Lys Pro
195 200 205

Glu Thr Ala Gly Thr Val Glu Leu Asp Asn Pro Phe Ile Leu Leu Val
210 215 220

Asp Lys Lys Ile Ser Asn Ile Arg Glu Leu Leu Pro Val Leu Glu Ala

225	230	235	240
Val Ala Lys Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Val Glu			
245		250	255
Gly Glu Ala Leu Ala Thr Leu Val Val Asn Thr Met Arg Gly Ile Val			
260	265		270
Lys Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala			
275	280	285	
Met Leu Gln Asp Ile Ala Ile Leu Thr Ala Gly Thr Val Ile Ser Glu			
290	295	300	
Glu Ile Gly Met Glu Leu Glu Lys Ala Thr Leu Glu Glu Leu Gly Gln			
305	310	315	320
Ala Lys Arg Val Val Ile Thr Lys Asp Asn Thr Thr Ile Ile Asp Gly			
325	330	335	
Ile Gly Asp Glu Ala Gln Ile Lys Ala Arg Val Val Gln Ile Arg Gln			
340	345	350	
Gln Ile Glu Asp Ser Thr Ser Asp Tyr Asp Lys Glu Lys Leu Gln Glu			
355	360	365	
Arg Val Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala			
370	375	380	
Ala Thr Glu Val Ala Met Lys Glu Lys Lys Asp Arg Val Asp Asp Ala			
385	390	395	400
Leu His Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly			
405	410	415	
Gly Val Ala Leu Val Arg Ala Ala Asn Lys Val Ser Ala Thr Leu Thr			
420	425	430	
Gly Asp Asn Glu Glu Gln Asn Val Gly Ile Lys Leu Ala Leu Arg Ala			
435	440	445	
Met Glu Ala Pro Leu Arg Gln Ile Val Glu Asn Ser Gly Glu Asp Ala			
450	455	460	
Ser Val Val Ala Arg Asp Val Lys Asp Gly Ser Gly Asn Phe Gly Tyr			
465	470	475	480
Asn Ala Thr Thr Glu Glu Tyr Gly Asp Met Leu Glu Met Gly Ile Leu			
485	490	495	
Asp Pro Thr Lys Val Thr Arg Ser Ala Leu Gln Phe Ala Ala Ser Ile			
500	505	510	
Ala Gly Leu Met Ile Thr Thr Glu Cys Met Ile Thr Asp Leu Pro Lys			
515	520	525	

Glu Asp Lys Leu Asp Ala Gln Ala Ala Met Gly Gly Met Gly Gly Met
530 535 540

Gly Gly Met Met
545

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 549 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Ala Lys Glu Leu Arg Phe Gly Asp Asp Ala Arg Leu Gln Met Leu
1 5 10 15

Ala Gly Val Asn Ala Leu Ala Asp Ala Val Gln Val Thr Met Gly Pro
20 25 30

Arg Gly Arg Asn Val Val Leu Glu Lys Ser Tyr Gly Ala Pro Thr Val
35 40 45

Thr Lys Asp Gly Val Ser Val Ala Lys Glu Ile Glu Phe Glu His Arg
50 55 60

Phe Met Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Ser Lys Thr
65 70 75 80

Ser Asp Thr Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Arg
85 90 95

Ser Ile Leu Val Glu Gly His Lys Ala Val Ala Ala Gly Met Asn Pro
100 105 110

Met Asp Leu Lys Arg Gly Ile Asp Lys Ala Val Leu Ala Val Thr Lys
115 120 125

Lys Leu Gln Ala Met Ser Lys Pro Cys Lys Asp Ser Lys Ala Ile Ala
130 135 140

Gln Val Gly Thr Ile Ser Ala Asn Ser Asp Glu Ala Ile Gly Ala Ile
145 150 155 160

Ile Ala Glu Ala Met Glu Lys Val Gly Lys Glu Gly Val Ile Thr Val
165 170 175

Glu Asp Gly Asn Gly Leu Glu Asn Glu Leu Ser Val Val Glu Gly Met

180	185	190
Gln Phe Asp Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Asn Asn Gln Gln		
195	200	205
Asn Met Ser Cys Glu Leu Glu His Pro Phe Ile Leu Leu Val Asp Lys		
210	215	220
Lys Val Ser Ser Ile Arg Glu Met Leu Ser Val Leu Glu Gly Val Ala		
225	230	240
Lys Ser Gly Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu		
245	250	255
Ala Leu Ala Thr Leu Val Val Asn Asn Met Arg Gly Ile Val Lys Val		
260	265	270
Cys Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu		
275	280	285
Gln Asp Ile Ala Ile Leu Thr Lys Gly Gln Val Ile Ser Glu Glu Ile		
290	295	300
Gly Lys Ser Leu Glu Gly Ala Thr Leu Glu Asp Leu Gly Ser Ala Lys		
305	310	320
Arg Ile Val Val Thr Lys Glu Asn Thr Thr Ile Ile Asp Gly Glu Gly		
325	330	335
Lys Ala Thr Glu Ile Asn Ala Arg Ile Thr Gln Ile Arg Ala Gln Met		
340	345	350
Glu Glu Thr Thr Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Val		
355	360	365
Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr		
370	375	380
Glu Val Glu Met Lys Glu Lys Lys Ala Arg Val Glu Asp Ala Leu His		
385	390	400
Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Val		
405	410	415
Ala Leu Ile Arg Ala Gln Lys Ala Leu Asp Ser Leu Lys Gly Asp Asn		
420	425	430
Asp Asp Gln Asn Met Gly Ile Asn Ile Leu Arg Arg Ala Ile Glu Ser		
435	440	445
Pro Met Arg Gln Ile Val Thr Asn Ala Gly Tyr Glu Ala Ser Val Val		
450	455	460
Val Asn Lys Val Ala Glu His Lys Asp Asn Tyr Gly Phe Asn Ala Ala		
465	470	480

Thr Gly Glu Tyr Gly Asp Met Val Glu Met Gly Ile Leu Asp Pro Thr
 485 490 495
 Lys Val Thr Arg Met Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Leu
 500 505 510
 Met Leu Thr Thr Glu Cys Met Val Ala Asp Leu Pro Lys Lys Glu Glu
 515 520 525
 Gly Val Gly Ala Gly Asp Met Gly Gly Met Gly Met Gly Gly Met
 530 535 540
 Gly Gly Met Met Glx
 545

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 541 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ala Lys Thr Ile Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu
 1 5 10 15
 Arg Gly Leu Asn Ala Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
 20 25 30
 Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile
 35 40 45
 Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro
 50 55 60
 Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr
 65 70 75 80
 Asp Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln
 85 90 95
 Ala Leu Val Arg Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro
 100 105 110
 Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Glu Lys Val Thr Glu
 115 120 125
 Thr Leu Leu Lys Ser Ala Lys Glu Val Glu Thr Lys Asp Gln Ile Ala

130	135	140
Ala Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile		
145	150	155
Ala Glu Ala Met Asp Lys Val Gly Asn Glu Gly Val Ile Thr Val Glu		
165	170	175
Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly Met Arg		
180	185	190
Phe Asp Lys Gly Tyr Ile Ser Gly Tyr Phe Val Thr Asp Ala Glu Arg		
195	200	205
Gln Glu Ala Val Leu Glu Asp Pro Phe Ile Leu Leu Val Ser Ser Lys		
210	215	220
Val Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu Lys Val Ile Gln		
225	230	235
Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala		
245	250	255
Leu Ser Thr Leu Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser Val		
260	265	270
Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln		
275	280	285
Asp Met Ala Ile Leu Thr Gly Gly Gln Val Ile Ser Glu Glu Val Gly		
290	295	300
Leu Ser Leu Glu Ser Ala Asp Ile Ser Leu Leu Gly Lys Ala Arg Lys		
305	310	315
Val Val Val Thr Lys Asp Glu Thr Thr Ile Val Glu Gly Ala Gly Asp		
325	330	335
Ser Asp Ala Ile Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile Glu		
340	345	350
Asn Ser Asp Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala		
355	360	365
Lys Leu Ala Gly Gly Val Ala Val Ile Lys Ala Gly Ala Ala Thr Glu		
370	375	380
Val Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp Ala Val Arg Asn		
385	390	395
Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Val Ala		
405	410	415
Leu Leu His Ala Ile Pro Ala Leu Asp Glu Leu Lys Pro Glu Gly Glu		
420	425	430

Glu Ala Thr Gly Ala Asn Ile Val Arg Val Ala Leu Glu Arg Pro Leu
 435 440 445
 Lys Gln Ile Ala Phe Asn Gly Gly Leu Glu Pro Gly Val Val Ala Glu
 450 455 460
 Lys Val Arg Asn Ser Pro Ala Gly Thr Gly Leu Asn Ala Ala Thr Gly
 465 470 475 480
 Glu Tyr Glu Asp Leu Leu Lys Ala Gly Ile Ala Asp Pro Val Lys Val
 485 490 495
 Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu Phe Leu
 500 505 510
 Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Ala Ala Ala Pro
 515 520 525
 Ala Gly Asp Pro Thr Gly Gly Met Gly Gly Met Asp Phe
 530 535 540

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 540 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Ala Lys Thr Ile Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu
 1 5 10 15
 Arg Gly Leu Asn Ala Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
 20 25 30
 Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile
 35 40 45
 Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro
 50 55 60
 Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr
 65 70 75 80
 Asp Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln
 85 90 95
 Ala Leu Val Arg Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro

100	105	110														
Leu	Gly	Leu	Lys	Arg	Gly	Ile	Glu	Lys	Ala	Val	Glu	Lys	Val	Thr	Glu	
115							120						125			
Thr	Leu	Leu	Lys	Gly	Ala	Lys	Glu	Val	Glu	Thr	Lys	Glu	Gln	Ile	Ala	
130							135						140			
Ala	Thr	Ala	Ala	Ile	Ser	Ala	Gly	Asp	Gln	Ser	Ile	Gly	Asp	Leu	Ile	
145							150						155			160
Ala	Glu	Ala	Met	Asp	Lys	Val	Gly	Asn	Glu	Gly	Val	Ile	Thr	Val	Glu	
	165						170						175			
Glu	Ser	Asn	Thr	Phe	Gly	Leu	Gln	Leu	Glu	Leu	Thr	Glu	Gly	Met	Arg	
	180						185						190			
Phe	Asp	Lys	Gly	Tyr	Ile	Ser	Gly	Tyr	Phe	Val	Thr	Asp	Pro	Glu	Arg	
	195						200						205			
Gln	Glu	Ala	Val	Leu	Glu	Asp	Pro	Tyr	Ile	Leu	Leu	Val	Ser	Ser	Lys	
	210						215						220			
Val	Ser	Thr	Val	Lys	Asp	Leu	Leu	Pro	Leu	Leu	Glu	Lys	Val	Ile	Gly	
	225						230						235			240
Ala	Gly	Lys	Pro	Leu	Leu	Ile	Ile	Ala	Glu	Asp	Val	Glu	Gly	Glu	Ala	
	245						250						255			
Leu	Ser	Thr	Leu	Val	Val	Asn	Lys	Ile	Arg	Gly	Thr	Phe	Lys	Ser	Val	
	260						265						270			
Ala	Val	Lys	Ala	Pro	Gly	Phe	Gly	Asp	Arg	Arg	Lys	Ala	Met	Leu	Gln	
	275						280						285			
Asp	Met	Ala	Ile	Leu	Thr	Gly	Gly	Gln	Val	Ile	Ser	Glu	Glu	Val	Gly	
	290						295						300			
Leu	Thr	Leu	Glu	Asn	Ala	Asp	Leu	Ser	Leu	Leu	Gly	Lys	Ala	Arg	Lys	
	305						310						315			320
Val	Val	Val	Thr	Lys	Asp	Glu	Thr	Thr	Ile	Val	Glu	Gly	Ala	Gly	Asp	
	325						330						335			
Thr	Asp	Ala	Ile	Ala	Gly	Arg	Val	Ala	Gln	Ile	Arg	Gln	Glu	Ile	Glu	
	340						345						350			
Asn	Ser	Asp	Ser	Asp	Tyr	Asp	Arg	Glu	Lys	Leu	Gln	Glu	Arg	Leu	Ala	
	355						360						365			
Lys	Leu	Ala	Gly	Gly	Val	Ala	Val	Ile	Lys	Ala	Gly	Ala	Ala	Thr	Glu	
	370						375						380			
Val	Glu	Leu	Lys	Glu	Arg	Lys	His	Arg	Ile	Glu	Asp	Ala	Val	Arg	Asn	
	385						390						395			400

Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Gly Val Thr
405 410 415

Leu Leu Gln Ala Ala Pro Thr Leu Asp Glu Leu Lys Leu Glu Gly Asp
420 425 430

Glu Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala Pro Leu
435 440 445

Lys Gln Ile Ala Phe Asn Ser Gly Leu Glu Pro Gly Val Val Ala Glu
450 455 460

Lys Val Arg Asn Leu Pro Ala Gly His Gly Leu Asn Ala Gln Thr Gly
465 470 475 480

Val Tyr Glu Asp Leu Leu Ala Ala Gly Val Ala Asp Pro Val Lys Val
485 490 495

Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu Phe Leu
500 505 510

Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Glu Lys Ala Ser
515 520 525

Val Pro Gly Gly Asp Met Gly Gly Met Asp Phe
530 535 540

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 537 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ser Lys Leu Ile Glu Tyr Asp Glu Thr Ala Arg His Ala Met Glu
1 5 10 15

Val Gly Met Asn Lys Leu Ala Asp Thr Val Arg Val Thr Leu Gly Pro
20 25 30

Arg Gly Arg His Val Val Leu Ala Lys Ala Phe Gly Gly Pro Thr Ile
35 40 45

Thr Asn Asp Gly Val Thr Val Ala Arg Glu Ile Asp Leu Glu Asp Pro
50 55 60

Phe Glu Asn Leu Gly Ala Gln Leu Val Lys Ser Val Ala Thr Lys Thr

65	70	75	80
Asn Asp Val Ala Gly Asp Gly Thr Thr Thr Ala Thr Val Leu Ala Gln			
85		90	95
Ala Leu Val Lys Gly Gly Leu Arg Met Val Ala Ala Gly Ala Asn Pro			
100		105	110
Val Ala Leu Gly Ala Gly Ile Ser Lys Ala Ala Asp Ala Val Ser Glu			
115		120	125
Ala Leu Leu Ala Val Ala Thr Pro Val Ala Gly Lys Asp Ala Ile Thr			
130		135	140
Gln Val Ala Thr Val Ser Ser Arg Asp Glu Gln Ile Gly Ala Leu Val			
145	150	155	160
Gly Glu Gly Met Asn Lys Val Gly Thr Asp Gly Val Val Ser Val Glu			
165		170	175
Glu Ser Ser Thr Leu Asp Thr Glu Leu Glu Phe Thr Glu Gly Val Gly			
180		185	190
Phe Asp Lys Gly Phe Leu Ser Ala Tyr Phe Val Thr Asp Phe Asp Ser			
195		200	205
Gln Gln Ala Val Leu Asp Asp Pro Leu Val Leu Leu His Gln Glu Lys			
210		215	220
Ile Ser Ser Leu Pro Glu Leu Leu Pro Met Leu Glu Lys Val Thr Glu			
225		230	240
Ser Gly Lys Pro Leu Leu Ile Val Ala Glu Asp Leu Glu Gly Glu Ala			
245		250	255
Leu Ala Thr Leu Val Val Asn Ser Ile Arg Lys Thr Leu Lys Ala Val			
260		265	270
Ala Val Lys Ser Pro Phe Phe Gly Asp Arg Arg Lys Ala Phe Leu Glu			
275		280	285
Asp Leu Ala Ile Val Thr Gly Gly Gln Val Val Asn Pro Glu Thr Gly			
290		295	300
Leu Val Leu Arg Glu Val Gly Thr Asp Val Leu Gly Ser Ala Arg Arg			
305		310	320
Val Val Val Ser Lys Asp Asp Thr Ile Ile Val Asp Gly Gly Ser			
325		330	335
Asn Asp Ala Val Ala Lys Arg Val Asn Gln Leu Arg Ala Glu Ile Glu			
340		345	350
Val Ser Asp Ser Glu Trp Asp Arg Glu Lys Leu Gln Glu Arg Val Ala			
355		360	365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Val Thr Glu
370 375 380

Thr Ala Leu Lys Lys Arg Lys Glu Ser Val Glu Asp Ala Val Ala Ala
385 390 395 400

Ala Lys Ala Ser Ile Glu Glu Gly Ile Ile Ala Gly Gly Ser Ala
405 410 415

Leu Val Gln Cys Gly Ala Ala Leu Lys Gln Leu Arg Thr Ser Leu Thr
420 425 430

Gly Asp Glu Ala Leu Gly Ile Asp Val Phe Phe Glu Ala Leu Lys Ala
435 440 445

Pro Leu Tyr Trp Ile Ala Thr Asn Ala Gly Leu Asp Gly Ala Val Val
450 455 460

Val Asp Lys Val Ser Gly Leu Pro Ala Gly His Gly Leu Asn Ala Ser
465 470 475 480

Thr Leu Gly Tyr Gly Asp Leu Val Ala Asp Gly Val Val Asp Pro Val
485 490 495

Lys Val Thr Arg Ser Ala Val Leu Asn Ala Ala Ser Val Ala Arg Met
500 505 510

Met Leu Thr Thr Glu Thr Ala Val Val Asp Lys Pro Ala Lys Thr Glu
515 520 525

Glu His Asp His His Gly His Ala His
530 535

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 541 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Ala Lys Thr Ile Ala Tyr Asp Glu Glu Ala Arg Arg Gly Leu Glu
1 5 10 15

Arg Gly Leu Asn Ser Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
20 25 30

Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile

35	40	45
Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro		
50	55	60
Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr		
65	70	75
Asp Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln		
85	90	95
Ala Leu Val Lys Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro		
100	105	110
Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Asp Lys Val Thr Glu		
115	120	125
Thr Leu Leu Lys Asp Ala Lys Glu Val Glu Thr Lys Glu Gln Ile Ala		
130	135	140
Ala Thr Ala Ala Ile Ser Ala Gly Asp Gln Ser Ile Gly Asp Leu Ile		
145	150	155
160		
Ala Glu Ala Met Asp Lys Val Gly Met Glu Gly Val Ile Thr Val Glu		
165	170	175
Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly Met Arg		
180	185	190
Phe Asp Lys Gly Tyr Ile Ser Gly Tyr Phe Val Thr Asp Ala Glu Arg		
195	200	205
Gln Glu Ala Val Leu Glu Glu Pro Tyr Ile Leu Leu Val Ser Ser Lys		
210	215	220
Val Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu Lys Val Ile Gln		
225	230	235
240		
Ala Gly Lys Ser Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu Ala		
245	250	255
Leu Ser Thr Leu Val Val Asn Lys Ile Arg Gly Thr Phe Lys Ser Val		
260	265	270
Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln		
275	280	285
Asp Met Ala Ile Leu Thr Gly Ala Gln Val Ile Ser Glu Glu Val Gly		
290	295	300
Leu Thr Leu Glu Asn Thr Asp Leu Ser Leu Leu Gly Lys Ala Arg Lys		
305	310	315
320		
Val Val Met Thr Lys Asp Glu Thr Thr Ile Val Glu Gly Ala Gly Asp		
325	330	335

Thr Asp Ala Ile Ala Gly Arg Val Ala Gln Ile Arg Thr Glu Ile Glu
 340 345 350

Asn Ser Asp Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala
 355 360 365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Ala Gly Ala Ala Thr Glu
 370 375 380

Val Glu Leu Lys Glu Arg Lys His Arg Ile Glu Asp Ala Val Arg Asn
 385 390 395 400

Ala Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Val Thr
 405 410 415

Leu Leu Gln Ala Ala Pro Ala Leu Asp Lys Leu Lys Leu Thr Gly Asp
 420 425 430

Glu Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu Glu Ala Pro Leu
 435 440 445

Lys Gln Ile Ala Phe Asn Ser Gly Met Glu Pro Gly Val Val Ala Glu
 450 455 460

Lys Val Arg Asn Leu Ser Val Gly His Gly Leu Asn Ala Ala Thr Gly
 465 470 475 480

Glu Tyr Glu Asp Leu Leu Lys Ala Gly Val Ala Asp Pro Val Lys Val
 485 490 495

Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly Leu Phe Leu
 500 505 510

Thr Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Thr Ala Ala Pro
 515 520 525

Ala Ser Asp Pro Thr Gly Gly Met Gly Met Asp Phe
 530 535 540

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 539 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Ser Lys Leu Ile Glu Tyr Asp Glu Thr Ala Arg Arg Ala Met Glu

1	5	10	15												
Val	Gly	Met	Asp	Lys	Leu	Ala	Asp	Thr	Val	Arg	Val	Thr	Leu	Gly	Pro
		20						25					30		
Arg	Gly	Arg	His	Val	Val	Leu	Ala	Lys	Ala	Phe	Gly	Gly	Pro	Thr	Val
		35						40				45			
Thr	Asn	Asp	Gly	Val	Thr	Val	Ala	Arg	Glu	Ile	Glu	Leu	Glu	Asp	Pro
	50				55					60					
Phe	Glu	Asp	Leu	Gly	Ala	Gln	Leu	Val	Lys	Ser	Val	Ala	Thr	Lys	Thr
	65					70			75			80			
Asn	Asp	Val	Ala	Gly	Asp	Gly	Thr	Thr	Thr	Ala	Thr	Ile	Leu	Ala	Gln
		85					90					95			
Ala	Leu	Ile	Lys	Gly	Gly	Leu	Arg	Leu	Val	Ala	Ala	Gly	Val	Asn	Pro
	100					105				110					
Ile	Ala	Leu	Gly	Val	Gly	Ile	Gly	Lys	Ala	Ala	Asp	Ala	Val	Ser	Glu
	115					120				125					
Ala	Leu	Leu	Ala	Ser	Ala	Thr	Pro	Val	Ser	Gly	Lys	Thr	Gly	Ile	Ala
	130					135			140						
Gln	Val	Ala	Thr	Val	Ser	Ser	Arg	Asp	Glu	Gln	Ile	Gly	Asp	Leu	Val
	145				150				155			160			
Gly	Glu	Ala	Met	Ser	Lys	Val	Gly	His	Asp	Gly	Val	Val	Ser	Val	Glu
		165				170				175					
Glu	Ser	Ser	Thr	Leu	Gly	Thr	Glu	Leu	Glu	Phe	Thr	Glu	Gly	Ile	Gly
		180				185				190					
Phe	Asp	Lys	Gly	Phe	Leu	Ser	Ala	Tyr	Phe	Val	Thr	Asp	Phe	Asn	
	195					200				205					
Gln	Gln	Ala	Val	Leu	Glu	Asp	Ala	Leu	Ile	Leu	Leu	His	Gln	Asp	Lys
	210					215			220						
Ile	Ser	Ser	Leu	Pro	Asp	Leu	Leu	Pro	Leu	Leu	Glu	Lys	Val	Ala	Gly
	225				230				235			240			
Thr	Gly	Lys	Pro	Leu	Leu	Ile	Val	Ala	Glu	Asp	Val	Glu	Gly	Glu	Ala
		245				250				255					
Leu	Ala	Thr	Leu	Val	Val	Asn	Ala	Ile	Arg	Lys	Thr	Leu	Lys	Ala	Val
		260				265			270						
Ala	Val	Lys	Gly	Pro	Tyr	Phe	Gly	Asp	Arg	Arg	Lys	Ala	Phe	Leu	Glu
	275					280				285					
Asp	Leu	Ala	Val	Val	Thr	Gly	Gly	Gln	Val	Val	Asn	Pro	Asp	Ala	Gly
	290					295			300						

Met Val Leu Arg Glu Val Gly Leu Glu Val Leu Gly Ser Ala Arg Arg
 305 310 315 320

Val Val Val Ser Lys Asp Asp Thr Val Ile Val Asp Gly Gly Thr
 325 330 335

Ala Glu Ala Val Ala Asn Arg Ala Lys His Leu Arg Ala Glu Ile Asp
 340 345 350

Lys Ser Asp Ser Asp Trp Asp Arg Glu Lys Leu Gly Glu Arg Leu Ala
 355 360 365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu
 370 375 380

Thr Ala Leu Lys Glu Arg Lys Glu Ser Val Glu Asp Ala Val Ala Ala
 385 390 395 400

Ala Lys Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Ala Ser
 405 410 415

Leu Ile His Gln Ala Arg Lys Ala Leu Thr Glu Leu Arg Ala Ser Leu
 420 425 430

Thr Gly Asp Glu Val Leu Gly Val Asp Val Phe Ser Glu Ala Leu Ala
 435 440 445

Ala Pro Leu Phe Trp Ile Ala Ala Asn Ala Gly Leu Asp Gly Ser Val
 450 455 460

Val Val Lys Lys Val Ser Glu Leu Pro Ala Gly His Gly Leu Asn Val
 465 470 475 480

Asn Thr Leu Ser Tyr Gly Asp Leu Ala Ala Asp Gly Val Ile Asp Pro
 485 490 495

Val Lys Val Thr Arg Ser Ala Val Leu Asn Ala Ser Ser Val Ala Arg
 500 505 510

Met Val Leu Thr Thr Glu Thr Val Val Val Asp Lys Pro Ala Lys Ala
 515 520 525

Glu Asp His Asp His His His Gly His Ala His
 530 535

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 545 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Ala Ala Lys Asp Val Gln Phe Gly Asn Glu Val Arg Gln Lys Met
1 5 10 15

Val Asn Gly Val Asn Ile Leu Ala Asn Ala Val Arg Val Thr Leu Gly
20 25 30

Pro Lys Gly Arg Asn Val Val Asp Arg Ala Phe Gly Gly Pro His
35 40 45

Ile Thr Lys Asp Gly Val Thr Val Ala Lys Glu Ile Glu Leu Lys Asp
50 55 60

Lys Phe Glu Asn Met Gly Ala Gln Met Val Lys Glu Val Ala Ser Lys
65 70 75 80

Thr Asn Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala
85 90 95

Gln Ser Ile Val Ala Glu Gly Met Lys Tyr Val Thr Ala Gly Met Asn
100 105 110

Pro Thr Asp Leu Lys Arg Gly Ile Asp Lys Ala Val Ala Ala Leu Val
115 120 125

Glu Glu Leu Lys Asn Ile Ala Lys Pro Cys Asp Thr Ser Lys Glu Ile
130 135 140

Ala Gln Val Gly Ser Ile Ser Ala Asn Ser Asp Glu Gln Val Gly Ala
145 150 155 160

Ile Ile Ala Glu Ala Met Glu Lys Val Gly Lys Glu Gly Val Ile Thr
165 170 175

Val Glu Asp Gly Lys Ser Leu Glu Asn Glu Leu Asp Val Val Glu Gly
180 185 190

Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Ile Asn Asp Ala
195 200 205

Glu Lys Gln Ile Ala Gly Leu Asp Asn Pro Phe Val Leu Leu Phe Asp
210 215 220

Lys Lys Ile Ser Asn Ile Arg Asp Leu Leu Pro Val Leu Glu Gln Val
225 230 235 240

Ala Lys Ala Ser Arg Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly
245 250 255

Glu Ala Leu Ala Thr Leu Val Val Asn Asn Ile Arg Gly Ile Leu Lys
260 265 270

Thr Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met
275 280 285

Leu Gln Asp Ile Ala Ile Leu Thr Gly Gly Thr Val Ile Ser Glu Glu
290 295 300

Val Gly Leu Ser Leu Glu Lys Ala Thr Leu Asp Asp Leu Gly Gln Ala
305 310 315 320

Lys Arg Ile Glu Ile Gly Lys Glu Asn Thr Thr Ile Ile Asp Gly Phe
325 330 335

Gly Asp Ala Ala Gln Ile Glu Ala Arg Val Ala Glu Ile Arg Gln Gln
340 345 350

Ile Glu Thr Ala Thr Ser Asp Tyr Asp Lys Glu Lys Leu Gln Glu Arg
355 360 365

Val Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala
370 375 380

Thr Glu Val Glu Met Lys Glu Lys Asp Arg Val Glu Asp Ala Leu
385 390 395 400

His Ala Thr Arg Ala Ala Val Glu Glu Gly Val Val Ala Gly Gly
405 410 415

Val Ala Leu Leu Arg Ala Arg Ala Leu Glu Asn Leu His Thr Gly
420 425 430

Asn Ala Asp Gln Asp Ala Gly Val Gln Ile Val Leu Arg Ala Val Glu
435 440 445

Ser Pro Leu Arg Gln Ile Val Ala Asn Ala Gly Gly Glu Pro Ser Val
450 455 460

Val Val Asn Lys Val Leu Glu Gly Lys Gly Asn Tyr Gly Tyr Asn Ala
465 470 475 480

Gly Ser Gly Glu Tyr Gly Asp Met Ile Glu Met Gly Val Leu Asp Pro
485 490 495

Ala Lys Val Thr Arg Ser Ala Leu Gln His Ala Ala Ser Ile Ala Gly
500 505 510

Leu Met Leu Thr Thr Asp Cys Met Ile Ala Glu Ile Pro Glu Glu Lys
515 520 525

Pro Ala Met Pro Asp Met Gly Gly Met Gly Gly Met Gly Gly Met Met
530 535 540

Glx
545

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 539 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Val Lys Gln Leu Lys Phe Ser Glu Asp Ala Arg Gln Ala Met Leu
1 5 10 15

Arg Gly Val Asp Gln Leu Ala Asn Ala Val Lys Val Thr Ile Gly Pro
20 25 30

Lys Gly Arg Asn Val Val Leu Asp Lys Glu Phe Thr Ala Pro Leu Ile
35 40 45

Thr Asn Asp Gly Val Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro
50 55 60

Tyr Glu Asn Met Gly Ala Lys Leu Val Gln Glu Val Ala Asn Lys Thr
65 70 75 80

Asn Glu Ile Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln
85 90 95

Ala Met Ile Gln Glu Gly Leu Lys Asn Val Thr Ser Gly Ala Asn Pro
100 105 110

Val Gly Leu Arg Gln Gly Ile Asp Lys Ala Val Lys Val Ala Val Glu
115 120 125

Ala Leu His Glu Asn Ser Gln Lys Val Glu Asn Lys Asn Glu Ile Ala
130 135 140

Gln Val Gly Ala Ile Ser Ala Ala Asp Glu Glu Ile Gly Arg Tyr Ile
145 150 155 160

Ser Glu Ala Thr Glu Lys Val Gly Asn Asp Gly Val Ile Thr Ile Ile
165 170 175

Thr Ile Glu Glu Ser Asn Arg Leu Asn Thr Glu Leu Glu Leu Gly Met
180 185 190

Gln Phe Asp Arg Gly Tyr Gln Ser Pro Tyr Met Val Thr Asp Ser Asp
195 200 205

Lys Met Val Ala Glu Leu Glu Arg Pro Tyr Ile Leu Val Thr Asp Lys
210 215 220

Lys Ile Ser Ser Phe Gln Asp Ile Leu Pro Leu Leu Glu Gln Val Val
225 230 235 240

Gln Ser Asn Arg Pro Ile Leu Ile Val Ala Asp Glu Val Glu Gly Asp
245 250 255

Ala Leu Thr Asn Ile Val Leu Asn Arg Met Arg Gly Thr Phe Thr Ala
260 265 270

Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu
275 280 285

Glu Asp Leu Ala Ile Leu Thr Gly Ala Gln Val Ile Thr Asp Asp Leu
290 295 300

Gly Leu Asp Leu Lys Asp Ala Ser Ile Asp Met Leu Gly Thr Ala Ser
305 310 315 320

Lys Val Glu Val Thr Lys Asp Asn Thr Thr Val Val Asp Gly Asp Gly
325 330 335

Asp Glu Asn Ser Ile Asp Ala Arg Val Ser Gln Leu Lys Ser Gln Ile
340 345 350

Glu Glu Thr Glu Ser Asp Phe Asp Arg Glu Lys Leu Gln Glu Arg Leu
355 360 365

Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Ser
370 375 380

Glu Thr Glu Leu Lys Glu Arg Lys Leu Arg Ile Glu Asp Ala Leu Asn
385 390 395 400

Ser Thr Arg Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Thr
405 410 415

Ala Leu Val Asn Val Tyr Gln Lys Val Ser Glu Asn Glu Ala Glu Gly
420 425 430

Asp Ile Glu Thr Gly Val Asn Ile Val Leu Lys Ala Leu Thr Ala Pro
435 440 445

Val Arg Gln Ile Ala Glu Asn Ala Gly Leu Glu Gly Ser Val Ile Val
450 455 460

Glu Arg Leu Lys Asn Ala Glu Pro Gly Val Gly Phe Asn Gly Ala Thr
465 470 475 480

Asn Glu Trp Val Asn Met Leu Arg Arg Gly Ile Val Asp Pro Thr Lys
485 490 495

Val Thr Arg Ser Ala Leu Gln His Ala Ala Ser Val Ala Ala Met Phe
500 505 510

Leu Thr Thr Glu Ala Val Val Ala Ser Ile Pro Glu Lys Asn Asn Asp
 515 520 525

Gln Pro Asn Met Gly Gly Met Pro Gly Met Met
 530 535

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 541 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Ala Lys Ser Ile Ile Tyr Asn Asp Glu Ala Arg Arg Ala Leu Glu
 1 5 10 15

Arg Gly Met Asp Ile Leu Ala Glu Ala Val Ala Val Thr Leu Gly Pro
 20 25 30

Lys Gly Arg Asn Val Val Leu Glu Lys Lys Phe Gly Ser Pro Gln Ile
 35 40 45

Ile Asn Asp Gly Ile Thr Ile Ala Lys Glu Ile Glu Leu Glu Asp His
 50 55 60

Val Glu Asn Thr Gly Val Ser Leu Ile Arg Gln Ala Ala Ser Lys Thr
 65 70 75 80

Asn Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala His
 85 90 95

Ala Ile Val Lys Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro
 100 105 110

Ile Ser Leu Lys Arg Gly Ile Asp Lys Ala Thr Asp Phe Leu Val Ala
 115 120 125

Arg Ile Lys Glu His Ala Gln Pro Val Gly Asp Ser Lys Ala Ile Ala
 130 135 140

Gln Val Gly Ala Ile Ser Ala Gly Asn Asp Glu Glu Val Gly Gln Met
 145 150 155 160

Ile Ala Asn Ala Met Asp Lys Val Gly Gln Glu Gly Val Ile Ser Leu
 165 170 175

Glu Glu Gly Lys Ser Met Thr Thr Glu Leu Glu Ile Thr Glu Gly Met
 180 185 190

Arg Phe Asp Lys Gly Tyr Ile Ser Pro Tyr Phe Val Thr Asp Ala Glu
195 200 205

Arg Met Glu Ala Val Leu Glu Asp Pro Arg Ile Leu Ile Thr Asp Lys
210 215 220

Lys Ile Asn Leu Val Gln Asp Leu Val Pro Ile Leu Glu Gln Val Ala
225 230 235 240

Arg Gln Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Ile Glu Lys Glu
245 250 255

Ala Leu Ala Thr Leu Val Val Asn Arg Leu Arg Gly Val Leu Asn Val
260 265 270

Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Gln Met Leu
275 280 285

Glu Asp Ile Ala Thr Leu Thr Gly Gly Gln Val Ile Ser Glu Asp Ala
290 295 300

Gly Leu Lys Leu Glu Ser Ala Thr Val Asp Ser Leu Gly Ser Ala Arg
305 310 315 320

Arg Ile Asn Ile Thr Lys Asp Asn Thr Thr Ile Val Ala Glu Gly Asn
325 330 335

Glu Ala Ala Val Lys Ser Arg Cys Glu Gln Ile Arg Arg Gln Ile Glu
340 345 350

Glu Thr Asp Ser Ser Tyr Asp Lys Glu Lys Leu Gln Glu Arg Leu Ala
355 360 365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu
370 375 380

Thr Glu Met Lys Asp Arg Lys Leu Arg Leu Glu Asp Ala Ile Asn Ala
385 390 395 400

Thr Lys Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Thr Thr
405 410 415

Leu Ala His Leu Ala Pro Gln Leu Glu Asp Trp Ala Thr Gly Asn Leu
420 425 430

Lys Asp Glu Glu Leu Thr Gly Ala Leu Ile Val Ala Arg Ala Leu Pro
435 440 445

Ala Pro Leu Lys Arg Ile Ala Glu Asn Ala Gly Gln Asn Gly Ala Val
450 455 460

Ile Ser Glu Arg Val Lys Glu Lys Glu Phe Asn Val Gly Tyr Asn Ala
465 470 475 480

Ala Ser Leu Glu Tyr Val Asp Met Leu Ala Ala Gly Ile Val Asp Pro
 485 490 495
 Ala Lys Val Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Gly
 500 505 510
 Met Val Leu Thr Thr Glu Cys Ile Val Val Asp Lys Pro Glu Lys Glu
 515 520 525
 Lys Ala Pro Ala Gly Ala Pro Gly Gly Asp Phe Asp Tyr
 530 535 540

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 552 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Ser Lys Leu Ile Ser Phe Lys Asp Glu Ser Arg Arg Ser Leu Glu
 1 5 10 15
 Ala Gly Ile Asn Ala Leu Ala Asp Ala Val Arg Ile Thr Leu Gly Pro
 20 25 30
 Lys Gly Arg Asn Val Leu Leu Glu Lys Gln Tyr Gly Ala Pro Gln Ile
 35 40 45
 Val Asn Asp Gly Ile Thr Val Ala Lys Glu Ile Glu Leu Ser Asn Pro
 50 55 60
 Glu Glu Asn Ala Gly Ala Lys Leu Ile Gln Glu Val Ala Ser Lys Thr
 65 70 75 80
 Lys Glu Ile Ala Gly Asp Gly Thr Thr Ala Thr Ile Ile Ala Gln
 85 90 95
 Ala Leu Val Arg Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro
 100 105 110
 Val Ala Leu Arg Arg Gly Ile Glu Lys Val Thr Thr Phe Leu Val Gln
 115 120 125
 Glu Ile Glu Ala Val Ala Lys Pro Val Glu Gly Ser Ala Ile Ala Gln
 130 135 140
 Val Ala Thr Val Ser Ser Gly Asn Asp Pro Glu Val Gly Ala Met Ile
 145 150 155 160

Ala Asp Ala Met Asp Lys Val Thr Lys Asp Gly Val Ile Thr Val Glu
165 170 175

Glu Ser Lys Ser Leu Asn Thr Glu Leu Glu Val Val Glu Gly Met Gln
180 185 190

Ile Asp Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Thr Asp Ser Asp Arg
195 200 205

Gln Leu Val Glu Phe Asp Asn Pro Leu Ile Leu Ile Thr Asp Lys Lys
210 215 220

Ile Ser Ala Ile Ala Glu Leu Val Pro Val Leu Glu Ala Val Ala Arg
225 230 235 240

Ala Gly Arg Pro Leu Leu Ile Ile Ala Glu Asp Ile Glu Gly Glu Ala
245 250 255

Leu Ala Thr Leu Val Val Asn Lys Ala Arg Gly Val Leu Asn Val Ala
260 265 270

Ala Ile Lys Ala Pro Ala Phe Gly Asp Arg Arg Lys Ala Val Leu Gln
275 280 285

Asp Ile Ala Ile Leu Thr Gly Gly Ser Val Ile Ser Glu Asp Ile Gly
290 295 300

Leu Ser Leu Asp Thr Val Ser Leu Asp Gln Leu Gly Gln Ala Val Lys
305 310 315 320

Ala Thr Leu Glu Lys Asp Asn Thr Ile Leu Val Ala Gly Ala Asp Lys
325 330 335

Arg Ala Ser Ala Gly Val Lys Glu Arg Ile Glu Gln Leu Arg Lys Glu
340 345 350

Tyr Ala Ala Ser Asp Ser Asp Tyr Asp Lys Glu Lys Ile Gln Glu Arg
355 360 365

Ile Ala Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala
370 375 380

Thr Glu Thr Glu Leu Lys Asp Arg Lys Leu Arg Ile Glu Asp Ala Leu
385 390 395 400

Asn Ala Thr Lys Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly
405 410 415

Thr Thr Leu Ile Arg Leu Ala Gly Lys Ile Glu Ser Phe Lys Ala Gln
420 425 430

Leu Ser Asn Asp Glu Glu Arg Val Ala Ala Asp Ile Ile Ala Lys Ala
435 440 445

Leu Glu Ala Pro Leu His Gln Leu Ala Ser Asn Ala Gly Val Glu Gly
 450 455 460
 Ser Val Ile Val Glu Lys Val Lys Glu Ala Thr Gly Asn Gln Gly Tyr
 465 470 475 480
 Asn Val Ile Thr Gly Lys Ile Glu Asp Leu Ile Ala Ala Gly Ile Ile
 485 490 495
 Asp Pro Ala Lys Val Val Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile
 500 505 510
 Ala Gly Met Val Leu Thr Thr Glu Ala Leu Val Val Glu Lys Pro Glu
 515 520 525
 Pro Ala Ala Pro Ala Met Pro Asp Met Gly Gly Met Gly Gly Met Gly
 530 535 540
 Gly Met Gly Gly Met Gly Met Met
 545 550

(2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 539 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Ala Lys Thr Ile Ala Phe Asp Lys Lys Ala Arg Arg Gly Leu Glu
 1 5 10 15
 Arg Gly Leu Asn Ala Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
 20 25 30
 Lys Gly Arg Asn Val Val Leu Glu Lys Lys Trp Gly Ala Pro Thr Ile
 35 40 45
 Thr Asn Asp Gly Val Ser Ile Ala Lys Glu Ile Glu Leu Glu Asp Pro
 50 55 60
 Tyr Glu Lys Ile Gly Ala Glu Leu Val Lys Glu Val Ala Lys Lys Thr
 65 70 75 80
 Asp Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln
 85 90 95
 Ala Leu Val Arg Glu Gly Leu Arg Asn Val Ala Ala Gly Ala Asn Pro
 100 105 110

Leu Gly Leu Lys Arg Gly Ile Glu Lys Ala Val Glu Ala Val Thr Glu
115 120 125

His Leu Leu Lys Ala Ala Lys Glu Val Glu Thr Lys Asp Gln Ile Ala
130 135 140

Ala Thr Ala Gly Ile Ser Ala Gly Asp Pro Ala Ile Gly Glu Leu Ile
145 150 155 160

Ala Glu Ala Met Asp Lys Val Gly Lys Glu Gly Val Ile Thr Val Glu
165 170 175

Glu Ser Asn Thr Phe Gly Leu Gln Leu Glu Leu Thr Glu Gly Met Arg
180 185 190

Phe Asp Lys Gly Phe Ile Ser Gly Tyr Phe Ala Thr Asp Ala Glu Arg
195 200 205

Gln Glu Ala Val Leu Glu Asp Pro Tyr Val Leu Leu Val Ser Gly Lys
210 215 220

Ile Ser Thr Val Lys Asp Leu Leu Pro Leu Leu Glu Lys Val Ile Gln
225 230 235 240

Ser Gly Lys Pro Leu Ala Ile Ile Ala Glu Asp Val Glu Gly Glu Ala
245 250 255

Leu Val Thr Leu Ile Val Asn Lys Ile Arg Gly Thr Phe Lys Ser Val
260 265 270

Ala Ile Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu Gln
275 280 285

Asp Met Ala Ile Leu Thr Gly Gly Gln Val Ile Ser Glu Glu Ile Gly
290 295 300

Leu Ser Leu Asp Thr Ala Gly Leu Glu Val Leu Gly Gln Ala Arg Gln
305 310 315 320

Val Val Val Thr Lys Asp Glu Thr Thr Ile Val Asp Gly Ala Gly Ser
325 330 335

Lys Glu Gln Ile Ala Gly Arg Val Ser Gln Ile Arg Ala Glu Ile Glu
340 345 350

Asn Ser Asp Ser Asp Tyr Asp Arg Glu Lys Leu Gln Glu Arg Leu Ala
355 360 365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Ala Gly Ala Ala Thr Glu
370 375 380

Asp Leu Lys Glu Arg Lys His Arg Ile Glu Asp Ala Val Arg Asn Ala
385 390 395 400

Lys Ala Ala Val Glu Glu Gly Ile Val Ala Gly Gly Ser Ser Leu
 405 410 415

Ala Gln Ser Gly Thr Val Phe Asp Ser Xaa Ala Leu Glu Gly Asp Glu
 420 425 430

Ala Thr Gly Ala Asn Ile Val Lys Val Ala Leu Asp Ala Pro Val Lys
 435 440 445

Gln Ile Ala Val Asn Ala Gly Leu Glu Pro Gly Val Val Ala Glu Lys
 450 455 460

Val Arg Asn Ser Pro Ala Gly Thr Gly Leu Asn Ala Ala Thr Gly Val
 465 470 475 480

Tyr Glu Asp Leu Leu Ala Ala Gly Ile Asn Asp Pro Val Lys Val Thr
 485 490 495

Arg Ser Ala Leu Gln Asn Ala Ala Ser Ile Ala Ala Leu Phe Leu Thr
 500 505 510

Thr Glu Ala Val Val Ala Asp Lys Pro Glu Lys Ala Gly Ala Pro Val
 515 520 525

Asp Pro Thr Gly Gly Met Gly Met Asp Phe
 530 535

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 582 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Val Ser Phe Leu Ser Ser Ser Val Ser Arg Leu Pro Leu Arg Ile
 1 5 10 15

Ala Gly Arg Arg Ile Pro Gly Arg Phe Ala Val Pro Gln Val Arg Thr
 20 25 30

Tyr Ala Lys Asp Leu Lys Phe Gly Val Asp Ala Arg Ala Ser Leu Leu
 35 40 45

Thr Gly Val Asp Thr Leu Ala Arg Ala Val Ser Val Thr Leu Gly Pro
 50 55 60

Lys Gly Arg Asn Val Leu Ile Asp Gln Pro Phe Gly Ser Pro Lys Ile
 65 70 75 80

Thr Lys Asp Gly Val Thr Val Ala Arg Ser Val Ser Leu Lys Asp Lys
 85 90 95

Phe Glu Asn Leu Gly Ala Arg Leu Val Gln Asp Val Ala Ser Lys Thr
 100 105 110

Asn Glu Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Thr Arg
 115 120 125

Ala Ile Phe Ser Glu Thr Val Arg Asn Val Ala Ala Gly Cys Asn Pro
 130 135 140

Met Asp Leu Arg Arg Gly Ile Gln Leu Ala Val Asp Asn Val Val Glu
 145 150 155 160

Phe Leu Gln Ala Asn Lys Arg Asp Ile Thr Thr Ser Glu Glu Ile Ser
 165 170 175

Gln Val Ala Thr Ile Ser Ala Asn Gly Asp Thr His Ile Gly Glu Leu
 180 185 190

Leu Ala Lys Ala Met Glu Arg Val Gly Lys Glu Gly Val Ile Thr Val
 195 200 205

Lys Glu Gly Arg Thr Ile Ser Asp Glu Leu Glu Val Thr Glu Gly Met
 210 215 220

Lys Phe Asp Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Thr Asp Val Lys
 225 230 235 240

Ser Gln Lys Val Glu Phe Glu Asn Pro Leu Ile Leu Leu Ser Glu Lys
 245 250 255

Lys Val Ser Ala Val Gln Asp Ile Leu Pro Ser Leu Glu Leu Ala Ala
 260 265 270

Gln Gln Arg Arg Pro Leu Val Ile Ile Ala Glu Asp Val Asp Gly Glu
 275 280 285

Ala Leu Ala Ala Cys Ile Leu Asn Lys Leu Arg Gly Gln Leu Gln Val
 290 295 300

Val Ala Ile Lys Ala Pro Gly Phe Gly Asp Asn Arg Arg Asn Met Leu
 305 310 315 320

Gly Asp Leu Ala Val Leu Thr Asp Ser Ala Val Phe Asn Asp Glu Ile
 325 330 335

Asp Val Ser Ile Glu Lys Ala Gln Pro His His Leu Gly Ser Cys Gly
 340 345 350

Ser Val Thr Val Thr Lys Glu Asp Thr Ile Ile Met Lys Gly Ala Gly
 355 360 365

Asp His Val Lys Val Asn Asp Arg Cys Glu Gln Ile Arg Gly Val Met
 370 375 380

Ala Asp Pro Asn Leu Thr Glu Ser Glu Lys Glu Lys Leu Gln Glu Arg
 385 390 395 400

Leu Ala Lys Leu Ser Gly Gly Ile Ala Val Ile Lys Val Gly Ala Ser
 405 410 415

Ser Glu Val Glu Val Asn Glu Lys Lys Asp Arg Ile Val Asp Ala Leu
 420 425 430

Asn Ala Val Lys Ala Ala Val Ser Glu Gly Val Leu Pro Gly Ala Gly
 435 440 445

Thr Ser Phe Val Lys Ala Ser Leu Arg Leu Gly Asp Ile Pro Thr Asn
 450 455 460

Asn Phe Asp Gln Lys Leu Gly Val Glu Ile Val Arg Lys Ala Ile Thr
 465 470 475 480

Arg Pro Ala Gln Thr Ile Leu Glu Asn Ala Gly Leu Glu Gly Asn Leu
 485 490 495

Ile Val Gly Lys Leu Lys Glu Leu Tyr Gly Lys Glu Phe Asn Ile Gly
 500 505 510

Tyr Asp Ile Ala Lys Asp Arg Phe Val Asp Leu Asn Glu Ile Gly Val
 515 520 525

Leu Asp Pro Leu Lys Val Val Arg Thr Gly Leu Val Asp Ala Ser Gly
 530 535 540

Val Ala Ser Leu Met Gly Thr Thr Glu Cys Ala Ile Val Asp Ala Pro
 545 550 555 560

Glu Glu Ser Lys Ala Pro Ala Gly Pro Pro Gly Met Gly Gly Met Gly
 565 570 575

Gly Met Pro Gly Met Met
 580

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 572 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Leu Arg Ser Ser Val Val Arg Ser Arg Ala Thr Leu Arg Pro Leu
1 5 10 15

Leu Arg Arg Ala Tyr Ser Ser His Lys Glu Leu Lys Phe Gly Val Glu
20 25 30

Gly Arg Ala Ser Leu Leu Lys Gly Val Glu Thr Leu Ala Glu Ala Val
35 40 45

Ala Ala Thr Leu Gly Pro Lys Gly Arg Asn Val Leu Ile Glu Gln Pro
50 55 60

Phe Gly Pro Pro Lys Ile Thr Lys Asp Gly Val Thr Val Ala Lys Ser
65 70 75 80

Ile Val Leu Lys Asp Lys Phe Glu Asn Met Gly Ala Lys Leu Leu Gln
85 90 95

Glu Val Ala Ser Lys Thr Asn Glu Ala Ala Gly Asp Gly Thr Thr Ser
100 105 110

Ala Thr Val Leu Gly Arg Ala Ile Phe Thr Glu Ser Val Lys Asn Val
115 120 125

Ala Ala Gly Cys Asn Pro Met Asp Leu Arg Arg Gly Ser Gln Val Ala
130 135 140

Val Glu Lys Val Ile Glu Phe Leu Ser Ala Asn Lys Lys Glu Ile Thr
145 150 155 160

Thr Ser Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala Asn Gly Asp
165 170 175

Ser His Val Gly Lys Leu Leu Ala Ser Ala Met Glu Lys Val Gly Lys
180 185 190

Glu Gly Val Ile Thr Ile Arg Glu Gly Arg Thr Leu Glu Asp Glu Leu
195 200 205

Glu Val Thr Glu Gly Met Arg Phe Asp Arg Gly Phe Ile Ser Pro Tyr
210 215 220

Phe Ile Thr Asp Pro Lys Ser Ser Lys Val Glu Phe Glu Lys Pro Leu
225 230 235 240

Leu Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Asp Ile Leu Pro
245 250 255

Ala Leu Glu Ile Ser Asn Gln Ser Arg Arg Pro Leu Leu Ile Ile Ala
260 265 270

Glu Asp Val Asp Gly Glu Ala Leu Ala Ala Cys Ile Leu Asn Lys Leu
275 280 285

Arg Gly Gln Val Lys Val Cys Ala Val Lys Ala Pro Gly Phe Gly Asp
 290 295 300
 Asn Arg Lys Asn Thr Ile Gly Asp Ile Ala Val Leu Thr Gly Gly Thr
 305 310 315 320
 Val Phe Thr Glu Glu Leu Asp Leu Lys Pro Glu Gln Cys Thr Ile Glu
 325 330 335
 Asn Leu Gly Ser Cys Asp Ser Ile Thr Val Thr Lys Glu Asp Thr Val
 340 345 350
 Ile Leu Asn Gly Ser Gly Pro Lys Glu Ala Ile Gln Glu Arg Ile Glu
 355 360 365
 Gln Ile Lys Gly Ser Ile Asp Ile Thr Thr Thr Asn Ser Tyr Glu Lys
 370 375 380
 Glu Lys Leu Gln Glu Arg Leu Ala Lys Leu Ser Gly Gly Val Ala Val
 385 390 395 400
 Ile Arg Val Gly Gly Ala Ser Glu Val Glu Val Gly Glu Lys Asp
 405 410 415
 Arg Tyr Asp Asp Ala Leu Asn Ala Thr Arg Ala Ala Val Glu Glu Gly
 420 425 430
 Ile Leu Pro Gly Gly Thr Ala Leu Val Lys Ala Ser Arg Val Leu
 435 440 445
 Asp Glu Val Val Val Asp Asn Phe Asp Gln Lys Leu Gly Val Asp Ile
 450 455 460
 Ile Arg Lys Ala Ile Thr Arg Pro Ala Lys Gln Ile Ile Glu Asn Ala
 465 470 475 480
 Gly Glu Glu Gly Ser Val Ile Ile Gly Lys Leu Ile Asp Glu Tyr Gly
 485 490 495
 Asp Asp Phe Ala Lys Gly Tyr Asp Ala Ser Lys Ser Glu Tyr Thr Asp
 500 505 510
 Met Leu Ala Thr Gly Ile Ile Asp Pro Phe Lys Val Val Arg Ser Gly
 515 520 525
 Leu Val Asp Ala Ser Gly Val Ala Ser Leu Leu Ala Thr Thr Glu Val
 530 535 540
 Ala Ile Val Asp Ala Pro Glu Pro Pro Ala Ala Ala Gly Ala Gly Gly
 545 550 555 560
 Met Pro Gly Gly Met Pro Gly Met Pro Gly Met Met
 565 570

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 577 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met	Ile	Ser	Thr	Leu	Arg	Gly	Lys	Ile	Phe	Asn	Asn	Gly	Ser	Asn	Arg
1								5			10				15
Asn Lys Cys Val Ser Ile Leu Ser Asn Ile Gln Lys Arg Asn Ile Ser															
		20				25						30			
Lys Asp Ile Arg Phe Gly Ser Asp Ala Arg Thr Ala Met Leu Thr Gly															
		35			40						45				
Cys Asn Lys Leu Ala Asp Ala Val Ser Val Thr Leu Gly Pro Lys Gly															
		50			55			60							
Arg Asn Val Ile Ile Glu Gln Ser Phe Gly Ser Pro Lys Ile Thr Lys															
		65			70			75			80				
Asp Gly Val Thr Val Ala Lys Ser Ile Glu Phe Asn Asn Lys Leu Ala															
		85			90						95				
Asn Leu Gly Ala Gln Met Val Lys Gln Val Ala Ala Asn Thr Asn Gly															
		100			105			110							
Lys Ala Gly Asp Gly Thr Thr Ala Thr Ile Leu Ala Arg Ser Ile															
		115			120			125							
Phe Gln Gln Gly Cys Lys Ala Val Asp Ser Gly Met Asn Pro Met Asp															
		130			135			140							
Leu Leu Arg Gly Ile Asn Lys Gly Val Glu Lys Val Leu Glu Tyr Leu															
		145			150			155			160				
Asn Ser Ile Lys Lys Asp Val Thr Thr Glu Glu Ile Phe Asn Val															
		165			170			175							
Ala Ser Ile Ser Asn Gly Asp Lys Asn Ile Gly Gln Leu Ile Ala Asp															
		180			185			190							
Thr Met Lys Lys Val Gly Lys Glu Gly Thr Ile Thr Val Thr Glu Gly															
		195			200			205							
Lys Thr Leu Gln His Glu Leu Glu Ile Val Glu Gly Ile Lys Phe Asp															
		210			215			220							

Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Asn Asn Ser Gln Lys Val Glu
225 230 235 240

Leu Asp Lys Pro Tyr Ile Leu Ile His Glu Lys Lys Ile Ser Thr Val
245 250 255

Lys Ser Leu Leu Pro Val Leu Glu His Val Leu Gln Asn Gln Ser Ser
260 265 270

Leu Leu Val Ile Ala Glu Asp Val Asp Ser Asp Ala Leu Ala Thr Leu
275 280 285

Ile Val Asn Lys Leu Arg Leu Gly Leu Lys Ile Cys Ala Val Lys Ala
290 295 300

Pro Gly Phe Gly Glu His Arg Lys Ala Leu Ile His Asp Ile Ala Val
305 310 315 320

Met Thr Gly Ala Lys Val Ile Thr Glu Glu Thr Gly Leu Lys Leu Asp
325 330 335

Asp Pro Gln Val Val Ser Tyr Leu Gly Lys Ala Lys Ser Ile Asn Val
340 345 350

Thr Lys Asp Ser Thr Leu Ile Met Glu Gly Glu Gly Lys Lys Glu Glu
355 360 365

Ile Asn Glu Arg Cys Glu Ser Ile Arg Asn Ala Ile Lys Met Asn Thr
370 375 380

Ser Asp Tyr Glu Lys Glu Lys Leu Gln Glu Arg Leu Ala Lys Ile Thr
385 390 395 400

Gly Gly Val Ala Leu Ile Lys Val Gly Gly Ile Ser Glu Val Glu Val
405 410 415

Asn Glu Ile Lys Asp Arg Ile Gln Asp Ala Leu Cys Ala Thr Lys Ala
420 425 430

Ala Val Glu Glu Gly Ile Val Pro Gly Gly Ser Ala Leu Leu Phe
435 440 445

Ala Ser Lys Glu Leu Asp Ser Val Gln Thr Asp Asn Tyr Asp Gln Arg
450 455 460

Val Gly Val Asn Ile Ile Lys Asp Ala Cys Lys Ala Pro Ile Lys Gln
465 470 475 480

Ile Ala Glu Asn Ala Gly His Glu Gly Ser Val Val Ala Gly Asn Ile
485 490 495

Leu Lys Asp Lys Asn Ser Asn Ile Gly Phe Asn Ala Gln Glu Gly Lys
500 505 510

Tyr Val Asp Met Ile Glu Ser Gly Ile Ile Asp Pro Thr Lys Val Val

515

520

525

Lys Thr Ala Ile Ser Asp Ala Ala Ser Ile Ala Ser Leu Met Thr Thr
 530 535 540

Thr Glu Val Ala Ile Val Asp Phe Lys Asp Ser Lys Asn Glu Glu Ser
 545 550 555 560

Ser Gln His Met Asn Ser Val Asn Ser Met Gly Asp Met Gly Gly Met
 565 570 575

Tyr

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 550 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Met Thr Asn Val Val Val Ser Gly Glu Gln Leu Gln Gln Ala Phe Arg
 1 5 10 15

Glu Val Ala Ala Val Ile Asp Ser Thr Val Ala Val Thr Ala Gly Pro
 20 25 30

Arg Gly Lys Thr Val Gly Ile Asn Lys Pro Tyr Gly Ala Pro Glu Ile
 35 40 45

Thr Lys Asp Gly Tyr Lys Val Met Lys Gly Ile Lys Pro Glu Lys Pro
 50 55 60

Leu Asn Ala Ala Ile Thr Ser Ile Phe Ala Gln Ser Cys Ser Gln Cys
 65 70 75 80

Asn Asp Lys Val Gly Asp Gly Thr Thr Cys Ser Ile Leu Thr Ser
 85 90 95

Gly Met Ile Val Glu Ala Ser Lys Ser Ile Ala Ala Gly Asn Asp Arg
 100 105 110

Ile Ser Ile Lys Asn Gly Met Gln Lys Ala Lys Asp Val Val Leu Lys
 115 120 125

Glu Val Ala Ser Met Ala Arg Thr Ile Ser Leu Glu Lys Ile Asp Glu
 130 135 140

Val Ala Gln Val Ala Ile Ile Ser Ala Asn Gly Asp Arg Ser Ile Gly
145 150 155 160

Ser Asn Ile Ala Asp Ala Val Lys Lys Val Gly Lys Glu Gly Val Ile
165 170 175

Thr Val Glu Glu Ser Lys Gly Ser Lys Glu Leu Glu Val Glu Leu Thr
180 185 190

Thr Gly Met Gln Phe Asp Arg Gly Tyr Leu Ser Pro Tyr Phe Ile Thr
195 200 205

Asn Asn Glu Lys Met Ile Val Glu Leu Asp Asp Pro Tyr Leu Leu Ile
210 215 220

Thr Glu Lys Lys Leu Asn Ile Ile Gln Pro Leu Leu Ser Ile Leu Glu
225 230 235 240

Ala Val Val Lys Ser Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Ile
245 250 255

Glu Gly Glu Ala Leu Ser Thr Leu Val Ile Asn Lys Leu Arg Gly Gly
260 265 270

Leu Lys Val Ala Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys
275 280 285

Glu Met Leu Glu Asp Ile Ala Ala Leu Thr Asn Ala Lys Tyr Val Ile
290 295 300

Lys Asp Glu Leu Gly Ile Lys Met Glu Asp Leu Thr Leu Glu Asp Leu
305 310 315 320

Gly Ile Ala Lys Asn Val Lys Ile Thr Lys Asp Asn Thr Thr Ile Val
325 330 335

Ser Glu Asn Arg Val Thr Asp Arg Val Lys Ala Arg Ile Glu Gln Ile
340 345 350

Lys Ser Gln Ile Glu Ser Ser Thr Ser Asp Tyr Asp Lys Glu Lys Leu
355 360 365

Arg Glu Arg Leu Ala Lys Leu Ser Gly Gly Val Ala Val Leu Lys Val
370 375 380

Gly Gly Ala Thr Glu Leu Glu Val Lys Glu Arg Arg Asp Arg Val Glu
385 390 395 400

Asp Gln Leu His Ala Thr Arg Ala Ala Ile Glu Glu Gly Ile Val Pro
405 410 415

Gly Gly Gly Val Ala Leu Leu Tyr Ala Ser Ser Ala Leu Asp Lys Leu
420 425 430

Lys Gly Ala Asp Asp Glu Glu Gln Ile Gly Ile Asn Ile Ile Lys Lys

435

440

445

Val Leu Ser Val Pro Ile Lys Arg Leu Val Lys Asn Ala Gly Leu Glu
 450 455 460

Ser Ala Val Ile Ile Asp Tyr Leu Ile Lys Gln Asn Asn Lys Glu Leu
 465 470 475 480

Ile Tyr Asn Val Glu Ala Met Ser Tyr Ala Asn Ala Phe Ala Ala Gly
 485 490 495

Val Ile Asp Pro Ala Lys Val Val Arg Ile Ala Phe Glu Thr Ala Ile
 500 505 510

Ser Val Ala Ser Val Leu Ile Thr Thr Glu Ser Met Ile Val Asp Ile
 515 520 525

Pro Asn Lys Asp Glu Asn Ala Ser Ser Pro Met Gly Ala Gly Gly Met
 530 535 540

Gly Arg Met Asn Asp Phe
 545 550

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 568 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Leu Arg Leu Ala Arg Lys Gly Leu Gln Thr Ala Val Val Arg Ser
 1 5 10 15

Tyr Ala Lys Asp Val Lys Phe Gly Ala Glu Gly Arg Gln Ala Met Leu
 20 25 30

Val Gly Val Asn Leu Leu Ala Asp Ala Val Ser Val Thr Met Gly Pro
 35 40 45

Lys Gly Arg Asn Val Ile Ile Glu Gln Ser Trp Gly Ser Pro Lys Ile
 50 55 60

Thr Lys Asp Gly Val Thr Val Ala Lys Ser Ile Asp Leu Lys Asp Lys
 65 70 75 80

Tyr Gln Asn Leu Gly Ala Lys Leu Ile Gln Asp Val Ala Asn Lys Ala
 85 90 95

Asn Glu Glu Ala Gly Asp Gly Thr Thr Cys Ala Thr Val Leu Thr Arg
100 105 110

Ala Ile Ala Lys Glu Gly Phe Glu Arg His Ser Ser Arg Gly Asn Ala
115 120 125

Val Glu Ile Arg Arg Gly Val Met Asn Ala Val Glu Val Val Val Ala
130 135 140

Glu Leu Lys Lys Ile Ser Lys Lys Val Thr Thr Pro Glu Glu Ile Ala
145 150 155 160

Gln Val Ala Thr Ile Ser Ala Asn Gly Asp Thr Val Val Gly Asn Leu
165 170 175

Ile Ser Asp Ala Met Lys Lys Val Gly Thr Thr Gly Val Ile Thr Val
180 185 190

Lys Asp Gly Lys Thr Leu Asn Asp Gln Leu Glu Leu Ile Glu Gly Met
195 200 205

Lys Phe Asp Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Thr Ser Ala Lys
210 215 220

Gly Ala Lys Val Glu Tyr Glu Lys Ala Leu Val Leu Leu Ser Glu Lys
225 230 235 240

Lys Ile Ser Gln Val Gln Asp Ile Val Pro Ala Leu Glu Leu Ala Asn
245 250 255

Lys Leu Arg Arg Pro Leu Val Ile Ile Ala Glu Asp Val Asp Gly Glu
260 265 270

Ala Leu Thr Thr Leu Val Leu Asn Arg Leu Lys Val Gly Leu Gln Val
275 280 285

Val Ala Ile Lys Ala Pro Gly Phe Gly Asp Asn Arg Lys Asn Ala Leu
290 295 300

Lys Asp Met Gly Ile Ala Thr Gly Ala Ser Ile Phe Gly Asp Glu Thr
305 310 315 320

Leu Asp Leu Arg Leu Glu Asp Ile Thr Ala Asn Asp Leu Gly Glu Val
325 330 335

Asp Glu Val Thr Ile Thr Lys Asp Asp Thr Leu Leu Leu Arg Gly Arg
340 345 350

Gly Asp Gln Thr Glu Ile Glu Lys Arg Ile Glu Glu Ile Thr Asp Glu
355 360 365

Ile Glu Arg Ser Thr Ser Asp Tyr Glu Lys Glu Leu Lys Leu Asn Glu Arg
370 375 380

Leu Ala Lys Leu Ser Lys Gly Val Ala Val Leu Lys Ile Gly Gly Gly

385	390	395	400
Ser Glu Val Glu Val Gly Glu Lys Lys Asp Arg Val Thr Asp Ala Leu			
405		410	415
Cys Ala Thr Arg Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Gly			
420	425		430
Val Ala Leu Leu Arg Ser Leu Thr Ala Leu Lys Asn Tyr Lys Ala Ala			
435	440		445
Asn Glu Asp Gln Gln Ile Gly Val Asn Ile Val Lys Lys Ala Leu Thr			
450	455		460
Gln Pro Ile Ala Thr Ile Val Lys Asn Ala Gly Leu Glu Pro Ser Ser			
465	470	475	480
Ile Ile Asp Glu Val Thr Gly Asn Ser Asn Thr Ser Tyr Gly Tyr Asp			
485		490	495
Ala Leu Asn Gly Lys Phe Val Asp Met Phe Glu Ala Gly Ile Ile Asp			
500	505		510
Pro Thr Lys Val Val Arg Thr Ala Leu Gln Asp Ala Ser Gly Val Ala			
515	520		525
Ser Leu Leu Ala Thr Thr Glu Cys Val Val Thr Glu Ile Pro Lys Glu			
530	535		540
Glu Ala Val Gly Gly Pro Ala Gly Gly Met Gly Gly Met Gly Gly Met			
545	550	555	560
Gly Gly Met Gly Gly Met Gly Phe			
565			

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 576 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Met Phe Arg Leu Pro Val Ser Leu Ala Arg Ser Ser Ile Ser Arg Gln			
1	5	10	15
Leu Ala Met Arg Gly Tyr Ala Lys Asp Val Arg Phe Gly Pro Glu Val			
20		25	30

Arg Ala Met Met Leu Gln Gly Val Asp Val Leu Ala Asp Ala Val Ala
35 40 45

Val Thr Met Gly Pro Lys Gly Arg Asn Val Ile Ile Glu Gln Ser Val
50 55 60

Gly Leu Ala Lys Ile Thr Lys Asp Gly Val Thr Val Ala Lys Ser Ile
65 70 75 80

Glu Leu Lys Asp Lys Phe Gln Asn Ile Gly Ala Lys Leu Val Gln Asp
85 90 95

Leu Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly Thr Thr Thr Ala
100 105 110

Thr Phe Leu Ala Arg Ala Ile Ala Lys Glu Gly Phe Glu Lys Ile Ser
115 120 125

Lys Gly Gly Asn Pro Val Glu Ile Arg Arg Gly Val Met Leu Ala Val
130 135 140

Glu Thr Val Lys Asp Asn Leu Lys Thr Met Ser Arg Pro Val Ser Thr
145 150 155 160

Pro Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala Asn Gly Asp Arg
165 170 175

Glu Ile Gly Asn Gly Lys Val Ser Val Ser Glu Ala Met Lys Lys Val
180 185 190

Gly Arg Asp Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Thr Asp
195 200 205

Glu Leu Glu Val Ile Glu Gly Thr Met Arg Phe Asp Arg Gly Tyr Ile
210 215 220

Ser Pro Tyr Phe Ile Asn Ser Ser Lys Gly Ala Lys Val Glu Phe Gln
225 230 235 240

Asp Ala Leu Leu Leu Ser Glu Lys Lys Ile Ser Ser Val Ala Glu
245 250 255

His His Ser Pro Leu Trp Arg Leu Ala Ser Arg Arg Thr Arg Lys Pro
260 265 270

Leu Val Ile Ile Ala Glu Asp Ile Asp Gly Glu Ala Leu Ser Thr Leu
275 280 285

Val Val Asn Arg Leu Lys Ile Gly Leu Gln Val Ala Ala Val Lys Ala
290 295 300

Pro Gly Phe Gly Asp Asn Arg Lys Ser Thr Leu Thr Asp Met Ala Thr
305 310 315 320

Ser Gly Gly Ile Val Phe Gly Asp Asp Val Ser Leu Val Lys Leu Glu

325	330	335
Asp Val Lys Val Ser Asp Leu Gly Gln Val Gly Glu Val Val Ile Thr		
340	345	350
Lys Asp Asp Thr Leu Leu Leu Lys Gly Lys Gly Lys Asp Asp Val		
355	360	365
Leu Arg Arg Ala Asn Gln Ile Arg Thr Lys Ile Glu Asp Thr Thr Ser		
370	375	380
Glu Tyr Glu Lys Glu Lys Leu Gln Glu Arg Leu Ala Arg Leu Ala Ser		
385	390	395
400		
Gly Val Ala Leu Arg Val Gly Gly Ser Ser Glu Val Glu Val Asn Glu		
405	410	415
Lys Lys Asp Arg Val His Asp Ala Leu Asn Ala Thr Arg Ala Ala Val		
420	425	430
Glu Glu Gly Ile Val Pro Gly Gly Arg Pro Leu Leu Arg Cys Ile		
435	440	445
Glu Lys Leu Glu Gly Val Glu Thr Thr Asn Glu Asp Gln Lys Leu Gly		
450	455	460
Val Glu Ile Val Arg Arg Ala Leu Arg Met Pro Cys Met Thr Ile Ala		
465	470	475
480		
Lys Asn Ala Gly Val Asp Gly Ala Met Val Val Ala Lys Val Glu Asn		
485	490	495
Gln Ala Gly Asp Tyr Gly Tyr Asp Ala Lys Gly Glu Tyr Gly Asn Leu		
500	505	510
Ile Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala Ile		
515	520	525
Thr Asp Ala Ser Gly Val Ala Ser Leu Leu Thr Thr Ala Glu Ala Val		
530	535	540
Val Thr Glu Ile Pro Lys Glu Asp Gly Ala Pro Ala Met Pro Gly Met		
545	550	555
560		
Gly Gly Met Met		
565	570	575

(2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 573 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Leu Arg Leu Pro Thr Val Phe Arg Gln Met Arg Pro Val Ser Arg
1 5 10 15

Val Leu Ala Pro His Leu Thr Arg Ala Tyr Ala Lys Asp Val Lys Phe
20 25 30

Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
35 40 45

Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
50 55 60

Glu Gln Gly Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
65 70 75 80

Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Lys Asn Ile Gly Ala Lys
85 90 95

Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
100 105 110

Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
115 120 125

Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
130 135 140

Met Leu Ala Val Asp Ala Val Ile Ala Glu Leu Lys Lys Gln Ser Lys
145 150 155 160

Pro Val Thr Thr Pro Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala
165 170 175

Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys
180 185 190

Val Gly Arg Lys Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Asn
195 200 205

Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile
210 215 220

Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln
225 230 235 240

Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser
245 250 255

Ile Val Pro Ala Leu Glu Ile Ala Asn Ala His Arg Lys Pro Leu Val
260 265 270

Ile Ile Ala Glu Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val Leu
275 280 285

Asn Arg Leu Lys Val Gly Leu Gln Val Val Ala Val Lys Ala Pro Gly
290 295 300

Phe Gly Asp Asn Arg Lys Asn Gln Leu Lys Asp Met Ala Ile Ala Thr
305 310 315 320

Gly Gly Ala Val Phe Gly Glu Gly Leu Thr Leu Asn Leu Glu Asp
325 330 335

Val Gln Pro His Asp Leu Gly Lys Val Gly Glu Val Ile Val Thr Lys
340 345 350

Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu
355 360 365

Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu
370 375 380

Tyr Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
385 390 395 400

Val Ala Val Leu Lys Val Gly Thr Ser Asp Val Glu Val Asn Glu
405 410 415

Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
420 425 430

Glu Glu Gly Ile Val Leu Gly Gly Cys Ala Leu Leu Arg Cys Ile
435 440 445

Pro Ala Leu Asp Ser Leu Thr Pro Ala Asn Glu Asp Gln Lys Ile Gly
450 455 460

Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala
465 470 475 480

Lys Asn Ala Gly Val Glu Gly Ser Leu Ile Val Glu Lys Ile Met Gln
485 490 495

Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn
500 505 510

Met Val Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala
515 520 525

Leu Leu Asp Ala Ala Gly Val Ala Ser Leu Leu Thr Thr Ala Glu Val
530 535 540

Val Val Thr Glu Ile Pro Lys Glu Glu Lys Asp Pro Gly Met Gly Ala

545	550	555	560
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Met	Gly	Gly	Met
565	Gly	Gly	Gly
	Met	Gly	Gly
	570		
			Phe

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 577 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met	Tyr	Arg	Phe
1			Ala
	Ser	Asn	Leu
		Ala	Ser
			Lys
			Ala
			Arg
			Ile
			Ala
			Gln

5	10	15
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Asn	Ala	Arg	Gln
20			Val
	Ser	Ser	Arg
			Met
			Ser
			Trp
			Ser
			Arg
			Asn
			Tyr
			Ala

25	30
----	----

Ala	Lys	Glu	Ile
35			Lys
		Phe	Gly
		Val	Glu
		Ala	Arg
			Ala
			Leu
			Met
			Leu
			Lys

40	45
----	----

Gly	Val	Glu	Asp
50			Leu
	Ala	Asp	Ala
		Val	Val
		Lys	Lys
		Val	Thr
			Met
			Gly
			Pro
			Lys

55	60
----	----

Gly	Arg	Asn	Val
65			Val
			Ile
			Glu
			Gln
			Ser
			Trp
			Gly
			Ala
			Pro
			Lys
			Val
			Thr

70	75	80
----	----	----

Lys	Asp	Gly	Val
85			Thr
	Ser	Val	Ala
		Lys	Lys
			Asp
			Lys
			Ile

90	95
----	----

Lys	Asn	Val	Gly
100			Ala
	Ser	Leu	Ser
		Val	
		Lys	Gln
		Val	Val
		Ala	Asn
			Ala
			Thr
			Asn

105	110
-----	-----

Asp	Val	Ala	Gly
115			Asp
			Gly
			Thr
			Thr
			Cys
			Ala
			Thr
			Val
			Leu
			Thr
			Arg
			Ala

120	125
-----	-----

Ile	Phe	Ala	Glu
130			Gly
			Cys
			Lys
			Ser
			Val
			Ala
			Ala
			Gly
			Met
			Asn
			Ala
			Met

135	140
-----	-----

Asp	Leu	Arg	Arg
145			Gly
			Ile
			Ser
			Met
			Ala
			Val
			Asp
			Ala
			Val
			Val
			Thr
			Asn

150	155	160
-----	-----	-----

Leu	Lys	Ser	Ala
165			Arg
			Met
			Ile
			Ser
			Thr
			Ser
			Glu
			Glu
			Ile
			Ala
			Gln

170	175
-----	-----

Val	Gly	Thr	Ile
180			Ser
			Ala
			Asn
			Gly
			Glu
			Arg
			Glu
			Ile
			Gly
			Glu
			Leu
			Ile

185	190
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Ala Lys Ala Met Glu Lys Val Gly Lys Glu Gly Val Ile Thr Ile Gln
195 200 205

Asp Gly Lys Thr Leu Phe Asn Glu Leu Glu Val Val Glu Gly Met Lys
210 215 220

Leu Asp Arg Gly Tyr Thr Ser Pro Tyr Phe Ile Thr Asn Gln Lys Thr
225 230 235 240

Gln Lys Cys Glu Leu Asp Asp Pro Leu Ile Leu Ile His Glu Lys Lys
245 250 255

Ile Ser Ser Ile Asn Ser Ile Val Lys Val Leu Glu Leu Ala Leu Lys
260 265 270

Arg Gln Arg Pro Leu Leu Ile Val Ser Glu Asp Val Glu Ser Asp Ala
275 280 285

Leu Ala Thr Leu Ile Leu Asn Lys Leu Arg Ala Gly Ile Lys Val Cys
290 295 300

Ala Ile Lys Ala Pro Gly Phe Gly Glu Asn Arg Lys Ala Asn Leu Gln
305 310 315 320

Asp Leu Ala Ala Leu Thr Gly Gly Glu Val Ile Thr Asp Glu Leu Gly
325 330 335

Met Asn Leu Glu Lys Val Asp Leu Ser Met Leu Gly Thr Cys Lys Lys
340 345 350

Val Thr Val Ser Lys Asp Asp Thr Val Ile Leu Asp Gly Ala Gly Asp
355 360 365

Lys Lys Gly Ile Glu Glu Arg Cys Glu Gln Ile Arg Ser Ala Ile Glu
370 375 380

Leu Ser Thr Ser Asp Tyr Asp Lys Glu Lys Leu Gln Glu Arg Leu Ala
385 390 395 400

Lys Leu Ser Gly Gly Val Ala Val Leu Lys Ile Gly Gly Ala Ser Glu
405 410 415

Ala Glu Val Gly Glu Lys Asp Arg Val Thr Asp Ala Leu Asn Ala
420 425 430

Thr Lys Ala Ala Val Glu Glu Gly Ile Leu Pro Gly Gly Val Ala
435 440 445

Leu Leu Tyr Ala Ala Arg Glu Leu Glu Lys Leu Pro Thr Ala Asn Phe
450 455 460

Asp Gln Lys Ile Gly Val Gln Ile Ile Gln Asn Ala Leu Lys Thr Pro
465 470 475 480

Val Tyr Thr Ile Ala Ser Asn Ala Gly Val Glu Gly Ala Val Ile Val

485

490

495

Gly Lys Leu Leu Glu Gln Asp Asn Pro Asp Leu Gly Tyr Asp Ala Ala
500 505 510

Lys Gly Glu Tyr Val Asp Met Val Lys Ala Gly Ile Ile Asp Pro Leu
515 520 525

Lys Val Ile Arg Thr Ala Leu Val Asp Ala Ala Ser Val Ser Ser Leu
530 535 540

Leu Thr Thr Thr Glu Ala Val Val Val Asp Leu Pro Lys Asp Glu Ser
545 550 555 560

Glu Ser Gly Ala Ala Gly Gly Met Gly Gly Met Val Val Met Asp
565 570 575

Tyr

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 576 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Tyr Arg Ala Ala Ser Leu Ala Ser Lys Ala Arg Gln Ala Gly
1 5 10 15

Ser Ser Ser Ala Ala Arg Gln Val Gly Ser Arg Leu Ala Trp Ser Arg
20 25 30

Asn Tyr Ala Ala Lys Asp Ile Lys Phe Gly Val Glu Ala Arg Ala Leu
35 40 45

Met Leu Arg Gly Val Glu Glu Leu Ala Asp Ala Val Lys Val Thr Met
50 55 60

Gly Pro Lys Gly Arg Asn Val Val Ile Glu Gln Ser Phe Gly Ala Pro
65 70 75 80

Lys Val Thr Lys Asp Gly Val Thr Val Ala Lys Ser Ile Glu Phe Lys
85 90 95

Asp Arg Val Lys Asn Val Gly Ala Ser Leu Val Lys Gln Val Ala Asn
100 105 110

Ala Thr Asn Asp Asn Ala Gly Asp Gly Thr Thr Cys Ala Thr Val Leu
115 120 125

Thr Lys Ala Ile Phe Thr Glu Gly Cys Lys Ser Val Ala Ala Gly Met
130 135 140

Asn Ala Met Asp Leu Arg Arg Gly Ile Ser Met Ala Val Asp Ala Val
145 150 155 160

Val Thr Asn Leu Lys Gly Met Ala Arg Met Ile Ser Thr Ser Glu Glu
165 170 175

Ile Ala Gln Val Gly Thr Ile Ser Ala Asn Gly Glu Arg Glu Ile Gly
180 185 190

Glu Leu Ile Ala Lys Ala Met Glu Lys Val Gly Lys Glu Gly Val Ile
195 200 205

Thr Ile Ala Asp Gly Asn Thr Leu Tyr Asn Glu Leu Glu Val Val Glu
210 215 220

Gly Met Lys Leu Asp Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Thr Asn
225 230 235 240

Ser Lys Ala Gln Lys Cys Glu Pro Glu Asp Pro Leu Ile Leu Ile His
245 250 255

Asp Arg Lys Val Thr Asn Met His Ala Val Val Lys Val Leu Glu Met
260 265 270

Ala Leu Lys Lys Gln Arg Pro Leu Leu Ile Val Ala Glu Asp Val Glu
275 280 285

Ser Glu Ala Leu Gly Thr Leu Ile Ile Asn Lys Leu Arg Ala Gly Ile
290 295 300

Lys Val Cys Ala Val Lys Ala Pro Gly Phe Gly Glu Asn Arg Lys Ala
305 310 315 320

Asn Leu Gln Asp Leu Ala Ile Leu Thr Gly Gly Glu Val Ile Thr Glu
325 330 335

Glu Leu Gly Met Asn Leu Glu Asn Val Glu Pro His Met Leu Gly Ser
340 345 350

Cys Lys Lys Val Thr Val Ser Lys Asp Asp Thr Val Ile Leu Asp Gly
355 360 365

Ala Gly Asp Lys Lys Ser Ile Glu Glu Arg Ala Asp Gln Ile Arg Ser
370 375 380

Ala Val Glu Asn Ser Thr Ser Asp Tyr Asp Lys Glu Lys Leu Gln Glu
385 390 395 400

Arg Leu Ala Lys Leu Ser Gly Gly Val Ala Val Leu Lys Ile Gly Gly

405	410	415
Ala Ser Glu Ala Glu Val Gly Glu Lys Lys Asp Arg Val Thr Asp Ala		
420	425	430
Leu Asn Ala Thr Lys Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly		
435	440	445
Gly Val Ala Leu Leu Tyr Ala Ser Lys Glu Leu Asp Lys Leu Gln Thr		
450	455	460
Ala Asn Phe Asp Gln Lys Ile Gly Val Gln Ile Ile Gln Asn Ala Leu		
465	470	480
Lys Thr Pro Val His Thr Ile Ala Ser Asn Ala Gly Val Glu Gly Ala		
485	490	495
Val Val Val Gly Lys Leu Leu Glu Gln Gly Asn Thr Asp Leu Gly Tyr		
500	505	510
Asp Ala Ala Lys Asp Glu Tyr Val Asp Met Val Lys Ala Gly Ile Ile		
515	520	525
Asp Pro Leu Lys Val Ile Arg Thr Ala Leu Val Asp Ala Ala Ser Val		
530	535	540
Ser Ser Leu Met Thr Thr Thr Glu Ser Ile Ile Val Glu Ile Pro Lys		
545	550	560
Glu Glu Ala Pro Ala Pro Ala Met Gly Gly Met Gly Gly Met Asp Tyr		
565	570	575

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 587 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Ala Ser Thr Asn Ala Leu Ser Ser Thr Ser Ile Leu Arg Ser Pro			
1	5	10	15
Thr Asn Gln Ala Gln Thr Ser Leu Ser Lys Lys Val Lys Gln His Gly			
	20	25	30
Arg Val Asn Phe Arg Gln Lys Pro Asn Arg Phe Val Val Lys Ala Ala			
	35	40	45

Ala Lys Asp Ile Ala Phe Asp Gln His Ser Arg Ser Ala Met Gln Ala
50 55 60

Gly Ile Asp Lys Leu Ala Asp Ala Val Gly Leu Thr Leu Gly Pro Arg
65 70 75 80

Gly Arg Asn Val Val Leu Asp Glu Phe Gly Ser Pro Lys Val Val Asn
85 90 95

Asp Gly Val Thr Ile Ala Arg Ala Ile Glu Leu Pro Asp Pro Met Glu
100 105 110

Asn Ala Gly Ala Ala Leu Ile Arg Glu Val Ala Ser Lys Thr Asn Asp
115 120 125

Ser Ala Gly Asp Gly Thr Thr Ala Ser Ile Leu Ala Arg Glu Ile
130 135 140

Ile Lys Leu Gly Leu Leu Asn Val Thr Ser Gly Ala Asn Pro Val Ser
145 150 155 160

Ile Lys Lys Gly Ile Asp Lys Thr Val Ala Ala Leu Val Glu Glu Leu
165 170 175

Glu Lys Leu Ala Arg Pro Val Lys Gly Gly Asp Asp Ile Lys Ala Val
180 185 190

Ala Thr Ile Ser Ala Gly Asn Asp Glu Leu Ile Gly Lys Met Ile Ala
195 200 205

Glu Ala Ile Asp Lys Val Gly Pro Asp Gly Val Leu Ser Ile Glu Ser
210 215 220

Ser Asn Ser Phe Glu Thr Thr Val Glu Val Glu Glu Gly Met Glu Ile
225 230 235 240

Asp Arg Gly Tyr Ile Ser Pro Gln Phe Val Thr Asn Pro Glu Lys Ser
245 250 255

Ile Val Glu Phe Glu Asn Ala Arg Val Leu Ile Thr Asp Gln Lys Ile
260 265 270

Ser Ala Ile Lys Asp Ile Ile Pro Leu Leu Glu Lys Thr Thr Gln Leu
275 280 285

Arg Ala Pro Leu Leu Ile Ile Ser Glu Asp Ile Thr Gly Glu Ala Leu
290 295 300

Ala Thr Leu Val Val Asn Lys Leu Arg Gly Ile Leu Asn Val Ala Ala
305 310 315 320

Ile Lys Ala Pro Gly Phe Gly Glu Arg Arg Lys Ala Leu Leu Gln Asp
325 330 335

Ile Ala Ile Leu Thr Gly Ala Glu Phe Gln Ala Ser Asp Leu Gly Leu
 340 345 350
 Leu Val Glu Asn Thr Thr Ile Glu Gln Leu Gly Leu Ala Arg Lys Val
 355 360 365
 Thr Ile Ser Lys Asp Ser Thr Thr Ile Ile Ala Asp Ala Ala Ser Lys
 370 375 380
 Asp Glu Leu Gln Ser Arg Val Ala Gln Leu Lys Lys Glu Leu Ser Glu
 385 390 395 400
 Thr Asp Ser Ile Tyr Asp Ser Glu Lys Leu Ala Glu Arg Ile Ala Lys
 405 410 415
 Leu Ser Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu Thr
 420 425 430
 Glu Leu Glu Asp Arg Lys Leu Arg Ile Glu Asp Ala Lys Asn Ala Thr
 435 440 445
 Phe Ala Ala Ile Glu Glu Gly Ile Val Pro Gly Gly Thr Ala Leu
 450 455 460
 Val His Leu Ser Gly Tyr Val Pro Ala Ile Lys Glu Lys Leu Glu Asp
 465 470 475 480
 Ala Asp Glu Arg Leu Gly Ala Asp Ile Val Gln Lys Ala Leu Val Ala
 485 490 495
 Pro Ala Ala Leu Ile Ala Gln Asn Ala Gly Ile Glu Gly Glu Val Val
 500 505 510
 Val Glu Lys Ile Lys Asn Gly Glu Trp Glu Val Gly Tyr Asn Ala Met
 515 520 525
 Thr Asp Thr Tyr Glu Asn Leu Val Glu Ser Gly Val Ile Asp Pro Ala
 530 535 540
 Lys Val Thr Arg Cys Ala Leu Gln Asn Ala Ala Ser Val Ala Gly Met
 545 550 555 560
 Val Leu Thr Thr Gln Ala Ile Val Val Glu Lys Pro Lys Pro Lys Ala
 565 570 575
 Ala Val Ala Ala Ala Pro Gln Gly Leu Thr Ile
 580 585

(2) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 545 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Ala Lys Asp Ile Lys Phe Gly Glu Glu Ala Arg Arg Ala Met Leu
1 5 10 15

Arg Gly Val Asn Ala Leu Ala Asp Ala Val Lys Val Thr Leu Gly Pro
20 25 30

Lys Gly Arg Asn Val Val Leu Glu Lys Ser Phe Gly Ala Pro Thr Ile
35 40 45

Thr Lys Asp Gly Val Thr Val Ala Lys Glu Ile Glu Leu Glu Asp Lys
50 55 60

Phe Glu Asn Met Gly Ala Gln Leu Val Lys Glu Val Ala Ser Lys Thr
65 70 75 80

Asn Asp Val Ala Gly Asp Gly Thr Thr Ala Thr Val Leu Ala Gln
85 90 95

Ala Ile Val Lys Glu Gly Leu Lys Asn Val Ala Ala Gly Ala Asn Pro
100 105 110

Met Asp Leu Arg Arg Gly Ile Asp Lys Ala Val Asp Ala Val Val Glu
115 120 125

Glu Leu Lys Ala Ile Ala Lys Pro Val Glu Thr Lys Glu Glu Ile Ala
130 135 140

Gln Val Ala Thr Ile Ser Ala Asn Gly Asp Glu Glu Ile Gly Glu Leu
145 150 155 160

Ile Ala Glu Ala Met Glu Lys Val Gly Lys Glu Gly Val Ile Thr Val
165 170 175

Glu Glu Gly Lys Thr Leu Glu Thr Glu Leu Glu Val Val Glu Gly Met
180 185 190

Gln Phe Asp Arg Gly Tyr Ile Ser Pro Tyr Phe Ile Thr Asp Ser Glu
195 200 205

Lys Gln Lys Ala Glu Leu Glu Asp Pro Leu Ile Leu Leu Thr Asp Lys
210 215 220

Lys Ile Ser Asn Ile Gln Asp Leu Leu Pro Val Leu Glu Glu Val Ala
225 230 235 240

Gln Ala Gly Lys Pro Leu Leu Ile Ile Ala Glu Asp Val Glu Gly Glu
245 250 255

Ala Leu Ala Thr Leu Val Val Asn Lys Leu Arg Gly Thr Leu Lys Val
260 265 270

Val Ala Val Lys Ala Pro Gly Phe Gly Asp Arg Arg Lys Ala Met Leu
275 280 285

Gln Asp Ile Ala Ile Leu Thr Gly Gly Gln Val Ile Ser Glu Glu Leu
290 295 300

Gly Leu Ser Leu Glu Asp Ala Thr Leu Glu Asp Leu Gly Gln Ala Lys
305 310 315 320

Lys Val Val Val Thr Lys Asp Asp Thr Thr Ile Val Asp Gly Ala Gly
325 330 335

Asp Ala Ala Ile Ala Gly Arg Val Ala Gln Ile Arg Ser Gln Ile Glu
340 345 350

Glu Ser Thr Ser Asp Tyr Asp Lys Glu Lys Leu Gln Glu Arg Leu Ala
355 360 365

Lys Leu Ala Gly Gly Val Ala Val Ile Lys Val Gly Ala Ala Thr Glu
370 375 380

Val Glu Leu Lys Glu Arg Lys Asp Arg Val Glu Asp Ala Leu Asn Ala
385 390 395 400

Thr Arg Ala Ala Val Glu Glu Gly Ile Val Pro Gly Gly Val Ala
405 410 415

Leu Leu Arg Ala Ala Pro Ala Leu Asp Lys Leu Lys Thr Glu Asn Gly
420 425 430

Asp Glu Ala Thr Gly Val Asn Ile Val Leu Arg Ala Leu Glu Ala Pro
435 440 445

Leu Arg Gln Ile Ala Glu Asn Ala Gly Leu Glu Gly Ser Val Val Val
450 455 460

Glu Lys Val Lys Asn Ser Glu Ala Gly Tyr Asn Ala Ala Thr Gly
465 470 475 480

Glu Tyr Val Asp Met Ile Ala Ala Gly Ile Ile Asp Pro Thr Lys Val
485 490 495

Thr Arg Ser Ala Leu Gln Asn Ala Ala Ser Val Ala Ser Leu Met Leu
500 505 510

Thr Thr Glu Ala Val Val Asp Lys Pro Glu Lys Glu Ala Ala Pro
515 520 525

Ala Gly Met Pro Gly Met Met Gly Gly Met Gly Gly Met Gly Gly Met
530 535 540

Met

545

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CATATGGCNG CNAAAGAYGT AAAA

24

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

TGATCACATC ATNCCNCCCA TNCC

24

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CATATGGCAA AAGAAATHAA RTTY

24

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 24 base pairs
- (B) TYPE: nucleic acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TGATCANCCN CCCATNCCNC CCAT

24

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GTAAAACGAC GGCCAG

16

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CAGGAAACAG CTATGAC

17

(2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CCAACCATCA CGAAAGA 17

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

ACGGGTCACT TTGGTTG 17

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

TTACTAATGA CGGGGTA 17

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TTACCAATGA CGGTGTG 17

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

ACAGGGTCAA TGATTCC

17

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

ACTGGATCAA TGATACC

17

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CCGTACCGTG CTCTGAC

17

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

ACCACGTTTC AGATCCA 17

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GACAGTTTCG CGGCAAC 17

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CTCAGAACGA AGATCAG 17

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GGTATGCAGT TCGACCG 17

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

CCGTGTTGGT CAAATCC

17

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

GGTAACTACG GTTACAA

17

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GAGGCCACTT CTTTCAC

17

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GGCTTCCAGC ACTGGCA

17

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

AACTTCAGTC GCAGCAC

17

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

CCTTGAAAGC CATTGCT

17

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GCTACACGTG CAGCCGT

17

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GCTGCAACAG GTGAGTG

17

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

TCATGAACAA TGGCTTG

17

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

ACGAAGCACA ATGTTAC

17

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

ATCACTAAAG ATGGTGT 17

(2) INFORMATION FOR SEQ ID NO:63:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

GCAGTTGCCG CAGCAGT 17

(2) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GCTACTCGTG CAGCTGT 17

(2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear